Medical Marijuana: What We Know and Don’t Know

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Dartmouth: Dept. of Medicine Grand Rounds
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Disclosures

- National Institute on Drug Abuse - NIH: 30 yrs of support
- Scientific Advisory Board: Center for Medical Cannabis Research, UCSD, State of California
- Consultation / DSMB: Tilray, Inc., GW Pharmaceuticals

Don’t Currently Use Cannabis - THC or CBD: 
recreationally or therapeutically
Do We Have a Cannabis/Marijuana “Crisis” in the U.S.?
21st Century Reefer Madness
Legalization & New Products
21st Century Reefer Madness
Legalization & New Products
Aims for this Morning

1) Addictive Potential / Consequences of Cannabis Use

2) “Medical” Marijuana / Cannabis: Operationalize?
   What are we talking about? Providers, Patients, Public
   What are you approving (Providers)?

3) Data on Therapeutic Cannabis Products?
   Scientific Literature, State Governments, Sales People?

4) Industry Impact? Koop Institute – Public Health Issues
• Drink Alcohol Regularly (one drink or more)
• Intoxicated (more than 4 drinks) past yr
• Why do you drink alcohol
• Use Marijuana/Cannabis (currently)
• Use Cannabis (past)
• Use CBD
• Think Alcohol Causes More Harm than Cannabis
• Why don’t you currently use Cannabis
Addictive Potential of Cannabis

Cannabis *(thc-laden)* is more similar than dissimilar to other substances that are considered “substances of abuse”

Like other substances, cannabis is used primarily for its positive (and negative) reinforcing effects

A subset of those who use will develop problems (10-30%)

Problems will range from mild to severe

Hasin et al., (2016); Haney et al. (2009)
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Prevalence of CUD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 - 17 years</td>
<td>2.2%</td>
</tr>
<tr>
<td>18 - 25 years</td>
<td>5.2%</td>
</tr>
<tr>
<td>26 + years</td>
<td>0.8%</td>
</tr>
</tbody>
</table>
NESARC 2012
Conditional Probability of Past Year CUD

NSDUH 2011
Conditional Probability of Past Year CUD

(Hasin et al., 2015)

(1 et al., 2014)
Cannabis Use Disorder (CUD)

• **DSM-5**: “Cannabis Use Disorder”
• **ICD 11**: “Cannabis”
  - “Hazardous Use”
  - “Harmful Use” (single episode, episodic, continuous)
  - “Cannabis Dependence”

• **Cannabis Withdrawal Disorder**

**CUD manifests much the same as other types of Substance Use Disorders** (Budney 2006, Shmulewitz, 2016)
Substance (Cannabis) Use Disorder Criteria

Impaired Control
(1) Longer / larger
(2) Quit / Control
(3) Time Spent
(4) Craving

Social Impairment
(5) Neglect roles, obligations
(6) Continued use despite associated interpersonal problems
(7) Reduced or Discontinued Activities
Substance (Cannabis) Use Disorder Criteria

Risky Use
(8) Use in Hazardous Situations

Physical/Psychological Consequences
(9) Continued use despite medical or psychological problems

Physiological/Pharmacological
(10) Withdrawal
(11) Tolerance
Cannabis Withdrawal?
Cannabis Withdrawal Syndrome (DSM-5)

3 or more within approximately 1 week:
- Irritability, anger, or aggression
- Nervousness or anxiety
- Sleep difficulty (e.g. insomnia, disturbing dreams)
- Decreased appetite or weight loss
- Restlessness
- Depressed mood
- At least 1 of the following *physical symptoms* cause significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills or headache
Cannabis Withdrawal Syndrome

• Similar to other substance withdrawal syndromes

• Clinically important

• Only a subset experience withdrawal and there are substantial individual differences

• No *serious* medical or psychological symptoms

(Budney et al., 2004, 2006; APA, 2013)
Self-reported Withdrawal Symptoms in CUD Adult Outpatients (Budney et al., 1999)

Severity >1  Severity >2

Percent of Patients

Crav  Irrit  Nerv  Restl  Depr  Sleep  Anger  Appet  H/A  Shaki
Timecourse: Withdrawal Discomfort Score

(Budney et al., 2003)
Pharmacological Specificity: Oral THC reduces Withdrawal Discomfort

(Budney, Vandrey, Moore, Hughes, 2007)
Cannabis and Tobacco Withdrawal are Comparable
(Vandrey et al., 2005; Vandrey et al. 2008, Budney et al., 2009)
U.S. Treatment Admissions
Primary Substance
TEDS Data (age 12 and above)
US Treatment Admissions
Primary Substance TEDS Data (12-17 years)

% of Total Admissions

<table>
<thead>
<tr>
<th>Year</th>
<th>Alcohol</th>
<th>Cannabis</th>
<th>Opiates</th>
<th>Cocaine</th>
<th>Cocaine</th>
<th>Cocaine</th>
<th>Cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td></td>
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<tr>
<td>2016</td>
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<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Legend:
- Alcohol
- Cannabis
- Opiates
- Cocaine
- Cocaine
- Cocaine

Graph shows the percentage of total admissions for each primary substance from 2002 to 2016.
Most Vulnerable Populations
Highest Rates of CUD / Experience Consequences

- Poverty --- Disadvantaged minorities, low SES
  - Reduction/Deprivation of Prosocial Reward
  - Increased Stress

- Psychiatric Disorders
  - perceived benefits, symptom relief

- Physical Disorders
  - perceived benefits, symptom relief
TAKE HOME

(1) Cannabis (THC-laden) is more similar than dissimilar to other substances that are considered “substances of abuse”

(2) Cannabis Use Disorder is Real

(3) CUD manifests much the same as other types of Substance Use Disorders
Aim 2
Operationalize “Medical” Marijuana / Cannabis
Cannabis Products: Smoking / Vaping
High Potency Products - Concentrates
Edibles
Lotions / Cremes / Salves / Patches
Vaping Delivery Devices
Aim 2
Operationalize “Medical” Marijuana / Cannabis

There is no such thing as “Medical Marijuana”!

Same plant and compounds as Recreational Marijuana

We do have FDA approved cannabinoid medicines:
- Marinol, Dronabinol (THC pills)
- Epidiolex (CBD oral solution)

Other countries have: Sativex (CBD/THC oramucosal spray)
Cannabis / Marijuana / Cannabinoids

What are we talking about?

• Is cannabis the same thing as marijuana?
• THC, CBD  THC/CBD ratio?
• What else in the plant/product is important?
• What are their effects? Interactions?
• What can cause harm? is safe? is therapeutic?
• How much of what …?
What is “active” in the Cannabis Plant?

- CBGA (Cannabigerolic acid)
- THCA ($\Delta^9$-tetrahydrocannabinolic acid)
- CBDA (Cannabidiolic acid)
- CBCA (Cannabichromenic acid)
- CBGVA (Cannabigerovarinic acid)
- THCVA (Tetrahydrocanabivarinic acid)
- CBDVA (Cannabidivarinic acid)
- CBCVA (Cannabichromevarinic acid)
- Terpenes: essential oils, smells, flavor
Delta-9 THC

** Primary psychoactive constituent

Dose related effects:

- High, euphoria
- Cognitive impairment (memory, learning, attention, time perspective, impaired judgment)
- Anxiety, Panic, Hallucinations, Psychosis?
- Analgesic, appetite stimulant, anti-nausea
Cannabidiol (CBD)

Cannabis plants have varying amounts of CBD

** May moderate the adverse effects of THC (anxiety, psychosis, and cognitive deficits)

** Demonstrated efficacy as an anti-epileptic
- “Potential” as an antipsychotic?
- “Potential” as an anxiolytic, anti-depressant, stress reduction, pain relief, anti-inflammatory, anti-cancer agent, Type 1 diabetes, etc., etc.
Entourage Effect:  
Mixture or Ratio of Compounds

Cannabis plants / products have varying amounts of all of these compounds.

How important are these?

Logically, combinations should have some effect, but these have not been studied well clinically.
Why Is Defining the “Product” so Important?
Example: “Marijuana and Breastfeeding…”
Mrouh et al., 2017

Human and animal data will be analyzed from 4 perspectives:
(1) the **effects of THC** on the mother in relation to lactation and care of the offspring,
(2) transfer of the chemical into breast milk,
(3) transfer to the offspring, and
(4) the indirect and direct **effects of THC** on the offspring.
What do we know about the compounds?

1) THC ≠ CBD ≠ CBG ≠ Cannabis/Marijuana
2) THC gets you high; CBD does not
3) CBG, CBV, CBC, CBD, --- ???
4) Dose matters, Route of Administration matters
TAKE HOME

When you are trying to understand/summarize the effects of cannabis/marijuana - positive or negative, you need to first define what you or the other person or the scientific article is talking about.

What was tested in that study or what did you take?
  THC
  CBD
  THC/CBD
  Other Cannabinoids
  Extracted / synthesized
  Smoked, Oral
  Dose
Aim 3: Data on Therapeutic Cannabis Products?
What has your state government told the public and you about these products / compounds?

What do those “dispensing” / selling / promoting these products act like they know?

What do they tell consumers / customers?
“While there are over 80 different cannabinoids in marijuana, only a handful have been researched and are known to provide positive effects on the human body.”

https://www.coloradopotguide.com/colorado-marijuana-blog/2015/march/31/the-positive-effects-of-cannabinoids/
NH Dispensary: Educate Yourself and Your Physician
NH Dispensary: Educate Yourself and Your Physician

**THC**
Tetrahydrocannabinol
THC is a psychoactive cannabinoid that may provide relief for patients with severe pain, nausea, poor appetite, and muscle spasms.

**CBD**
Cannabidiol
CBD is a non-psychoactive cannabinoid that may provide relief for patients with severe, persistent muscle spasms, severe pain, and agitation of Alzheimer’s Disease.

**CBC**
Cannabichromene
CBC is a non-psychoactive cannabinoid that may help relieve severe pain, inhibit cell growth in tumors, promote bone growth, and reduce inflammation.

**THCV**
Tetrahydrocannabinorvin
THCV is a psychoactive cannabinoid that may help suppress appetite, reduce seizures, and may promote bone growth.

**CBG**
Cannabigerol
CBG is a non-psychoactive cannabinoid that may help slow bacteria growth, inhibit cell growth in tumors, promote bone growth, and reduce inflammation.

**CBN**
Cannabinol
CBN is a non-psychoactive cannabinoid that may provide relief for patients with agitation of Alzheimer’s Disease, severe pain, and muscle spasms.
# NH Approved Conditions for Therapeutic Use of Cannabis

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Conditions</th>
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<tbody>
<tr>
<td>AIDS or / HIV+</td>
<td>Spinal Cord Injury or Disease</td>
</tr>
<tr>
<td>Alzheimer’s Disease</td>
<td>Traumatic Brain Injury (TBI)</td>
</tr>
<tr>
<td>Amyotrophic Lateral Sclerosis (ALS)</td>
<td>Ulcerative Colitis</td>
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<tr>
<td>Cachexia</td>
<td>Moderate to Severe Pain</td>
</tr>
<tr>
<td>Cancer</td>
<td>Moderate to Severe PTSD</td>
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<tr>
<td>Chronic Pancreatitis</td>
<td>&gt;1 injuries that interferes with daily activities as documented by the patient’s provider</td>
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<tr>
<td>Crohn’s Disease</td>
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<td>Epilepsy</td>
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<td>Glaucoma</td>
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<td>Hepatitis C Lupus</td>
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<tr>
<td>Multiple Sclerosis (MS)</td>
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<td>Muscular Dystrophy</td>
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<tr>
<td>Parkinson’s Disease</td>
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<td><strong>UNDER CONSIDERATION:</strong></td>
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<tr>
<td></td>
<td>Insomnia</td>
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<td></td>
<td>Anxiety</td>
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<td></td>
<td>Opioid Use Disorder</td>
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<td>Tick-Bourne Illnesses</td>
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</tbody>
</table>
Content of Active Compounds (THC/CBD) in Cannabis Products

e.g.: One Dispensary in New Hampshire

**Plant Material / Flowers** *
THC: 0.6% - 30.6%*
CBD: 0.04% - 14.6%*

**Concentrates (Oils, Tinctures, Wax, Patches)**
THC: 35.3% - 87.5%**
CBD: 0.01% - 40.3%**

**Edibles**
THC: 20mg – 100mg**
CBD: 20mg

**Capsules**
THC 5-50mg
CBD 5-25mg
Content of Active Compounds (THC/CBD/CBG)
One Dispensary in New Hampshire

FLOWER
$20 (1G), $55 (1/8 OZ), $100 (¼ OZ), $190 (½ OZ), $360 (OZ)

CBD-RICH
Known for its non-psychoactive qualities, CBD has been reported to be beneficial for its analgesic, anti-inflammatory properties

AC CBD-Rich
Cannabinoid Profile: 0.60% THC | 13.90% CBD | <0.12% CBG
SS1:1: 1:1 CBD:THC
Cannabinoid Profile: 5.8% THC | 7.5% CBD | 0.14% CBG
• **FLOWER**

• **THC-RICH**
  • C99: Sativa: 22.60% **THC** | <0.12% CBD | 0.13% CBG
  • BbK: Indica. 23.2% **THC** | <0.12% CBD | 0.8% CBG
  • PN: Sativa: 25.70% **THC** | <0.12% CBD | <0.12% CBG
  • BV: Hybrid 16.5% **THC** | <0.12% | 2.7% CBG
  • GG#4: Hybrid 24.7% **THC** | <0.12% CBD | 0.30% CBG
  • **20% off all week!!!**

• **PRE-ROLLS (0.5 GRAM PRJS) **AVAILABLE IN 10 PACKS**
  • 1 PRE-ROLL......$8  7 PRE-ROLLS.....$46  **10 PACK (SINGLE STRAIN).....$65**
CONCENTRATES

ROSIN

A SOLVENT FREE EXTRACT, ROSIN IS CREATED BY HEAT AND PRESSURE. KNOWN FOR POTENCY, IT'S BEST TO START LOW AND SLOW WITH THIS WAXY CONCENTRATE.

PN: 62.9% THC | <0.1% CBD | 3.19% CBG

COLD BREW CONCENTRATE PREMIUM

C99: 84% THC | <0.1% CBD | 0.4% CBG
BbK: 82.6% THC | <0.1% CBD | 2.2% CBG
GG#4: 81.4% THC | <0.1% CBD | 1.27% CBG
PN: 65.7% THC | <0.1% CBD | 1.44% CBG
Which of these products is good for each of the approved medical conditions?

*** Your State does not provide that information

How much THC, CBD, ratio of each, CBG

How much should you take of each?

How often should you take it? For how long?

Should you smoke it? Vape it? Eat it? Drop it on your tongue? Or rub it on?
What Do We Know from Scientific Studies?
National Academy of Sciences


https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state
Current data and summaries are confusing

“Potential” is clear:  biological plausibility - yes
laboratory models - yes
pre-clinical demonstrations - yes
case reports /open label - sometimes
controlled clinical data - almost never
Evidence Modifiers
(NAS 2017)

There is **conclusive** evidence…
There is **moderate** evidence…
There is **limited** evidence…
There is **no or insufficient evidence** to support or refute …
There is **substantial evidence** of a statistical association between cannabis use and…
Cannabis use does not appear to increase the likelihood of developing depression, anxiety, and posttraumatic stress disorder.

Regular cannabis use is likely to increase the risk for developing social anxiety disorder.

** There is limited evidence that cannabis or cannabinoids are effective for: improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol)

LIMITED Evidence for Therapeutic Effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest. For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

This review identified one randomized trial with a high risk of bias that compared a single 600 mg dose of cannabidiol to a placebo in 24 participants (undergraduate students) with generalized social anxiety disorder.
This review identified one randomized trial with a high risk of bias that compared a single 600 mg dose of cannabidiol to a placebo in 24 participants (undergraduate students) with generalized social anxiety disorder.

Cannabidiol was associated with a greater improvement on the anxiety factor of a 100-point visual analogue mood scale (mean difference from baseline −16.52, p = 0.01) compared with a placebo during a simulated public speaking test. (Bergamaschi et al., 2011)

DOSE: single 600mg CBD

What is being sold:
25mg CBD Capsules. $80 pack of 10
CBD-Rich Tincture 400mg (10ml). $90 400mg per bottle *1 drop = 1mg
CBD Dosing

Social Anxiety Study. single dose: 600mg CBD
Epidiolex Trial: 10-20mg/kg
100lbs (45kg): 450 to 900mg CBD day
Hurd et al. lab testing 400-600mg doses

What is being sold:
25mg CBD Capsules. $80 pack of 10
CBD-Rich Tincture 400mg per bottle *1 drop=1mg $90
THC Dosing and Pain

Ware et al. (2010) RCT Chronic Neuropathic Pain

9.4% THC (25mg) 3-5x per day with is equivalent to 2.5mg dose or 7.5-12mg per day

Result: Lowered pain score (0-10 scale) by 0.7 pts (6.1 to 5.4 compared to placebo)

What is being sold:

By Prescription: 2.5-5 mg tablets of dronabinol or marinol (prescription)

Cannabis Dispensary:

- Plant Material THCs: 0.6% - 30.6%
- Concentrates THCs: 35.3% - 87.5%
- Edibles THCs: 20mg – 100mg
- Capsules THCs: 5-50mg
Therapeutic Effects and the Evidence?

Standards of Evidence?
Terminology for Communicating about Evidence?
Potential for Adverse Effects?
Specificity: Compound, Dose, Route of Administration
Recommendations?
“Potential” “Promising”

Communicating about (and researching) the Benefits requires a major shift in how we discuss effects and report scientific findings.
How Do You Communicate?

Lack of Evidence?
Specificity of Findings?
Potential for Placebo Effects?
Magnitude of Effects (efficacy)?
Symptom Relief vs. “Cure” vs. Treatment

*** DHMC workgroup lead by Cynthia Reuter:
Therapeutic Cannabis Guidance Statement
Aim 4: Cannabis Industry Impact
Cannabis Business and Industry

**Forbes**

Spending on legal cannabis worldwide is expected to hit $57 billion by 2027

North America, going from $9.2 billion in 2017 to $47.3 billion a decade later

**Marijuana Business Daily**

Marijuana executives offer strategies and insights on salaries and recruitment

**Weekly Deal Watch: Cultivation and retail continues to dominate M&A cannabis activity**

Published May 23, 2019

The cannabis cultivation and retail sector has become increasingly crowded and competitive, but successful operators can still make themselves attractive acquisition targets. [READ MORE >](#)
The Cannabis Lobby

The Cannabis Trade Federation (CTF) has hired 15 lobbyists to push the Strengthening the Tenth Amendment Through Entrusting States Act

Joint effort: cannabis lobby heads to Washington to woo US lawmakers

Industry leaders descended on the capital this week amid hopes the country at large is slowly embracing legalization.
The Market
How to Recommend Sexual Cannabis Products to an Inquisitive Customer
Cannabis Industry: “Big Pharma”?

Internet Headline:
“Infusing marijuana with data: Cannabis industry vets aim to clear the haze in a booming industry”

…as they plotted their next endeavor, one word kept coming up in almost every conversation: **data**

…yet hardly anyone knew, at least when it came to numbers,

**what do consumers liked most**
Cannabis Industry: “Big Pharma”?

*Headset* is part of a wave of new firms trying to bring the kinds of consumer metrics enjoyed by big brands such as Coca-Cola, Toyota and Nestle to cannabis.

The legal recreational pot business in the U.S. is expected to reach $7 billion this year, a 28 percent increase over 2018…pumping money into an industry that is attracting tech workers from the likes of Microsoft, Apple and Amazon who are leaping into the trade and bringing their data-based marketing skills.
The public is being lead to believe cannabis/marijuana is good for everything that ails you, and that it is relatively harmless.

Many of the conditions/disorders that have been approved as appropriate for use of “medical” cannabis include conditions that make one vulnerable to developing a substance use disorder.
Perceived Risks and Benefits?
College Freshman and Sophomores (n > 1000) (2018)

Cannabis has therapeutic benefit for:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Depression</td>
<td>71-86%</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>68-94%</td>
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<tr>
<td>ADHD</td>
<td>31-54%</td>
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<tr>
<td>PTSD</td>
<td>51-80%</td>
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<tr>
<td>Pain</td>
<td>80-95%</td>
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</tbody>
</table>
• Politicians / Legislatures have decided to inform the public that Marijuana/Cannabis is a medicine that can help with just about everything –

• They have let the Industry (sales people) inform the consumer (patient / vulnerable population) what product / dose / route is best for them.

• Cannabis Industry is booming!!!!
Cannabis Regulatory Science and Policy

• Mitigate harm, maximize benefit
• Keep Industry impact under control
• Protect the public and those most vulnerable
Science and Common Sense

Thanks for Listening!