Cannabis Use and Cannabis Use Disorder in the Setting of Legalization

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Cannabis Question 1

FDA-approved indications include:

1. Insomnia related to PTSD
2. Glaucoma
3. Seizure disorder
4. N/V 2/2 to chemo, wasting related to HIV
5. Chronic pain/spasticity 2/2 multiple sclerosis
Cannabis Question 2

Past year use is highest in:

1. Age 12-17
2. Age 18-25
3. Age 26-35
4. Age 36-45
Cannabis Question 3

Risk of use disorder shown to be associated with:
1. Parental attitudes towards use
2. Early onset (adolescent) use
3. Route of administration
4. Regular/daily use
No conflicts of interest to disclose
Objectives

- Epidemiology
- Comorbidity
- Neurobiology
- Management Policy
- Clinical Presentation

Case
Case: TJ

- Forty-three yo navy veteran, PTSD, depression, MST, borderline traits, AUD (severe) in remission, impulse control/anger issues.
- **Sertraline** 300mg PO daily
- **Prazosin** 15mg PO QHS
- **Quetiapine** 300mg PO BID
- **Trazodone** 150mg PO QHS
- "Vapes" hash oil and consumes edible (brownie) daily.
“Everyone smokes pot. Welcome to San Francisco.”
Epidemiology: Cannabis Use

- Most commonly used illegal substance worldwide
- Lifetime prevalence in U.S. 42-46%
- Past year use highest in young adults 18-25
- Past year CUD highest ages 21-26
- Abuse/dep: 1.5% (2001) → 2.9% (2012)
- Greater increases in use and CUD in MML states vs non-MML

(Hasin JAMA 2017; DuPont 2014, UpToDate, )
Epidemiology: Cannabis Use

Past-Month Use of Selected Illicit Drugs

(SAMHSA NSDUH survey 2013)
Epidemiology: Cannabis Use

First Specific Drug Associated with Initiation of Illicit Drug Use 2013

- Marijuana, 70.3%
- Pain Relievers, 12.5%
- Inhalants, 6.3%
- Tranquilizers, 5.2%
- Stimulants, 2.7%
- Hallucinogens, 2.6%
- Sedatives, 0.2%
- Cocaine, 0.1%

2.8 million initiates of illicit drugs

(SAMHSA NSDUH survey 2013)
Epidemiology: Cannabis Use

Percent of Students Reporting Daily Use of Marijuana, by Grade

SOURCE: University of Michigan, 2015 Monitoring the Future Study

(UMich/NIDA MTF Study 2016)
Epidemiology: Cannabis Use

Percent Disapproval of Smoking Marijuana Regularly

SOURCE: University of Michigan, 2015 Monitoring the Future Study

(UMich/NIDA MTF Study 2016)
Comorbidity

“A lot of people with mental issues smoke pot.”
Comorbidity: SUD

- N = 34653 NESARC respondents.
- Cannabis use
  - SUD (OR 6.2)
  - CUD (OR 9.5)
  - AUD (OR 2.7)
  - Nicotine dep (OR 1.7)

Not significant: new mood or anxiety dx.

(Blanco 2016, JAMA)
Comorbidity: Mood and Anxiety

Mood & Anxiety Disorders Among Respondents with Marijuana Dependence (NESARC)

(NESARC 2014)
Comorbidity: Sub-populations?

(Buckner 2012, Drug Alc Dep)
### Among n = 462 Adolescent Cannabis Users

<table>
<thead>
<tr>
<th>Substance use diagnosis</th>
<th>OR Dependent vs. Non-dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol abuse</td>
<td>2.09 (1.14, 3.82)</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>1.18 (0.64, 2.19)</td>
</tr>
<tr>
<td>Opioid abuse</td>
<td>0.37 (0.13, 1.05)</td>
</tr>
<tr>
<td>Opioid dependence</td>
<td>0.76 (0.43, 1.35)</td>
</tr>
<tr>
<td>Stimulant abuse</td>
<td>1.74 (0.38, 8.05)</td>
</tr>
<tr>
<td>Stimulant dependence</td>
<td>0.82 (0.21, 3.18)</td>
</tr>
<tr>
<td>Cocaine abuse</td>
<td>1.14 (0.31, 4.22)</td>
</tr>
<tr>
<td>Cocaine dependence</td>
<td>2.25 (0.50, 10.13)</td>
</tr>
<tr>
<td>Benzodiazepine abuse</td>
<td>0.77 (0.23, 2.52)</td>
</tr>
<tr>
<td>Benzodiazepine dependence</td>
<td>1.58 (0.34, 7.37)</td>
</tr>
<tr>
<td>Hallucinogen dependence</td>
<td>1.56 (0.18, 13.61)</td>
</tr>
</tbody>
</table>

(Zaman 2015, J Addict Med)
### Comorbidity: Adolescents

Among n = 462 Adolescent Cannabis Users

<table>
<thead>
<tr>
<th>Psychiatric diagnosis</th>
<th>OR Dependent vs. Non-dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any depressive disorder</td>
<td>1.41(0.69, 2.89)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>1.25(0.26, 6.02)</td>
</tr>
<tr>
<td>Mood Disorder NOS</td>
<td>1.84(1.00, 3.37)</td>
</tr>
<tr>
<td>ADHD</td>
<td>2.06(1.08, 3.92)</td>
</tr>
<tr>
<td>Any behavioral disorder</td>
<td>2.43(0.82, 7.16)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>0.62(0.06, 6.91)</td>
</tr>
<tr>
<td>Any psychiatric disorder</td>
<td>2.15(1.22, 3.78)</td>
</tr>
<tr>
<td>≥2 psychiatric disorders</td>
<td>1.96(1.12, 3.41)</td>
</tr>
</tbody>
</table>

(Zaman 2015, J Addict Med)
Cannabis and Psychosis:

- Increased risk of psychotic outcome
- Dose dependent risk
- Speeds psychosis onset by 7 years
- Higher paranoia, hospitalizations
- Lower brain volume

(Moore 2007, Lancet)
“It’s labeled like a medication. So I know exactly what I’m getting.”
Trichomes
Chemical Composition

CBD  THCa  CBG  CBC  CBN  THCv  CBDa

Tetrahydrocannabinol (THC)  Cannabidiol (CBD)
Neurobiology

Plant-derived cannabinoid

Presynaptic neuron

↓Ca^{2+}

Endogenous cannabinoids

NEUROTRANSMITTERS

AEA or 2-AG

Postsynaptic neuron

↑Activity (for example, ↑Ca^{2+} concentration)

Nature Reviews | Cancer
Marijuana’s Effects on the Brain

When marijuana is smoked, its active ingredient, THC, travels throughout the body, including the brain, to produce its many effects. THC attaches to sites called cannabinoid receptors on nerve cells in the brain, affecting the way those cells work. Cannabinoid receptors are abundant in parts of the brain that regulate movement, coordination, learning and memory, higher cognitive functions such as judgment, and pleasure.

(NIDA/Scientific American)
Neurobiology

Brain matures (myelinates) from back to front

- 12-14 Cerebellum (motor)
- 14-18 Limbic (social or emotional)
- 18-26 Frontal (thinking or cognition)


Adapted from D.Pating, SFVAMC 11/16
Neurobiology

Adapted from D.Pating, SFVAMC 11/16
### Cognition

**Summary of Research Findings on the Effects of Cannabis on Executive Functions**

<table>
<thead>
<tr>
<th>Executive Function</th>
<th>Acute Effects</th>
<th>Residual Effects</th>
<th>Long-Term Effects</th>
</tr>
</thead>
</table>
| Attention/Concentration          | Impaired (light use)  
Normal (heavy use) | Mixed findings | Largely normal    |
| Decision Making and Risk Taking  | **Mixed findings** | **Impaired**     | **Impaired**      |
| Inhibition/Impulsivity           | Impaired                      | Mixed findings   | Mixed findings    |
| Working Memory                   | Impaired                      | Normal           | Normal            |
| Verbal Fluency                   | Normal                        | Mixed findings   | Mixed findings    |

*Note: Acute = 0-6 hours after use; Residual = 7hr -20d after use; Long-term = ≥3wks.*
Adolescent Use and Cognition

(Meier 2012, PNAS)
Adolescent Use and Cognition

- Age of onset, frequency, amount affect cog performance
- Earlier onset <-> More use, poorer cog
- Structural, functional differences in brains of users
- Conclusion: **Exposure during vulnerable period** → **altered brain development**

(Batalla 2013, PLoS One; Gruber 2012, Psychol Addict Beh)
Adolescent Use and Outcomes

Age- and dose-dependent impact on:
- High-school completion
- Attainment of university degree
- Cannabis dependence
- Illicit drugs
- Suicide attempt
- Depression
- Welfare dependence

(Silins 2014, Lancet Psychiatry)
## Preparations

<table>
<thead>
<tr>
<th>Preparations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana^a</td>
<td>Dried plant product consisting of leaves, stems, and flowers; typically smoked or vaporized</td>
</tr>
<tr>
<td>Hashish</td>
<td>Concentrated resin cake that can be ingested or smoked</td>
</tr>
<tr>
<td>Tincture^a</td>
<td>Cannabinoid liquid extracted from plant; consumed sublingually</td>
</tr>
<tr>
<td>Hashish oil</td>
<td>Oil obtained from cannabis plant by solvent extraction; usually smoked or inhaled; butane hash oil (sometimes referred to as “dabs”), for example</td>
</tr>
<tr>
<td>Infusion^a</td>
<td>Plant material mixed with nonvolatile solvents such as butter or cooking oil and ingested</td>
</tr>
</tbody>
</table>

^a These preparations are available from state-approved medical marijuana dispensaries.

(Hill 2015, JAMA)
Pair tied to butane hash oil explosion in Astoria accused of assault

Updated on May 5, 2017 at 4:57 PM, Posted on May 5, 2017 at 4:04 PM

Two men involved in a butane-related explosion in Astoria last fall were arraigned in Clatsop County Court Friday on felony assault charges, including one that comes with a mandatory 70 month sentence. (Danny

(The Oregonian)
Dispensaries
Preparations
Preparations

You will live on a beach and smoke pot
Preparations
Labeling (in)accuracy

Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products

Ryan Vandrey, PhD1; Jeffrey C. Raber, PhD2; Mark E. Raber2; Brad Douglass, PhD3; Cameron Miller, MS3; Marcel O. Bonn-Miller, PhD4

[+] Author Affiliations

Addiction to Cannabis

“You can’t really get hooked on it like the other stuff.”
Cannabis intoxication

Impairment + 2 symptoms within 2 hours

(DSM 5)
NEW YORK -- We were reminded again of the nightmare of drug abuse Tuesday when synthetic marijuana seemed to turn people into zombies on a New York City street.

It was a bizarre scene: Dozens of people with blank stares stumbling around a Brooklyn neighborhood. Brian Arthur live-streamed it on Facebook.

"As I was walking up a block, I see anybody laying out on the floor, and everybody’s just stumbling all over the place," Arthur said. "It looked like a scene out of a zombie movie."

Emergency workers sent 33 people to area hospitals, saying they appeared to be under the influence of synthetic marijuana. (CBS news reports)
Cannabis withdrawal

Three within 1 week:

- Irritability, anger or aggression
- Anxiety
- Sleep difficulty
- Decreased appetite or w/l
- Restlessness
- Depressed mood
- At least one: abd pain, shakiness/ tremors, sweating, fever, chills, or headache

(DSM 5)
# Cannabis Withdrawal Scale

(Allsop 2011, PLoS One; NIDA)

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>Moderately</th>
<th>Extremely</th>
<th>Negative impact on daily activity (0 – 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 The only thing I could think about was smoking some cannabis</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>2 I had a headache</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>3 I had no appetite</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>4 I felt nauseous (like vomiting)</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>5 I felt nervous</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>6 I had some angry outbursts</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>7 I had mood swings</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>8 I felt depressed</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>9 I was easily irritated</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>10 I had been imagining being stoned</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>11 I felt restless</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>12 I woke up early</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>13 I had a stomach ache</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>14 I had nightmares and/or strange dreams</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>15 Life seemed like an uphill struggle</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>16 I woke up sweating at night</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>17 I had trouble getting to sleep at night</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>18 I felt physically tense</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
<tr>
<td>19 I had hot flashes</td>
<td>0 1 2 3</td>
<td>4 5 6 7</td>
<td>8 9 10</td>
<td></td>
</tr>
</tbody>
</table>
Cannabis Use Disorder

Two within 12 months:

- Larger amounts, longer than intended
- Persistent/unsuccesful cut down
- A great deal of time spent
- Cravings
- Failure at major obligations
- Persistent social/interpersonal impairment.
- Important activities reduced
- Recurrent use in hazardous situations
- Use despite consequences
- Tolerance
- Withdrawal

(DSM 5)
CUDIT-R

- Eight questions, 0-4 points each.
- Scores $\geq 8 = \text{hazardous cannabis use.}$
- Scores $\geq 12 = \text{possible CUD, speak with expert.}$
Use to Addiction

All users $\rightarrow$ 9% addicted.

Adolescent users $\rightarrow$ 17% addicted.

Daily users $\rightarrow$ 25-50% addicted.

(NIDA Drug Facts 2012)
Case: TJ

Travelled to Iowa

Five days after cessation:

- Anxiety/outbursts
- Insomnia
- Tremors
- Insomnia
- PTSD symptoms/isolation → home
Treatment: Pharmacology

- **Mason BJ 2012: RCT, n=50**
  - *Gabapentin* 1200mg daily vs Placebo
  - *Gabapentin* = less +UDS, decreased w/d

- **Gray KM 2012: RCT, n=116 adolescents**
  - *NAC* 1200mg BID vs Placebo
  - *NAC* = more negative UDS

(Mason 2012, Gray 2012)
Treatment: Pharmacology

- Levin FR 2011: RCT, n=156,
  - Dronabinol 20mg BID vs Placebo
  - Dronabinol = higher retention, decreased w/d

- Allsop DJ 2014: RCT, n=51
  - Nabiximols (~80mg:80mg TCH:CBD) vs Placebo
  - Nabiximols = higher retention, decreased w/d

(Levin 2011, Allsop 2014)
Treatment: Behavioral

No one best modality, good evidence for:

- Cognitive Behavioral Therapy
- Motivational interviewing
- Contingency Management
- Group therapy

(DuPont 2014, UpToDate)
Case: TJ- Outcome

“I don’t want to stop. It’s a good treatment for my PTSD. But we can keep an eye on it.”
“Medical” Marijuana

Psychiatric:
- APA 2013: No current psychiatric indications, but more study warranted

Non-psychiatric:
- Nausea, vomiting related to chemo
- Anorexia/Wasting related to HIV

(APA 2013; Abramowicz 2017 JAMA)
“Medical” Marijuana

- Epilepsy
  - Early evidence for childhood, rx-resistant epilepsy
  - Insufficient evidence for other seizure d/o

- Specific pain syndromes
  - Chronic pain: 6 studies, n = 325
  - Neuropathic pain: 6 studies, n = 396

- Spasticity from Multiple Sclerosis
  - Twelve studies, n = 1600

(Abramowicz 2017 JAMA ; Hill 2015 JAMA)
LET'S GET IT RIGHT, CALIFORNIA:
Adult Use of Marijuana Act

Join the AUMA coalition to pass the consensus statewide ballot measure to control, regulate and tax adult use of marijuana while protecting kids.

Your Email Address  Zip Code  SUBMIT
Cannabis Question 1

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Past year use is highest in:

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Risk of use disorder shown to be associated with:
1. Parental attitudes towards use
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3. Route of administration
4. Regular/daily use
Cannabis Question 3

Risk of use disorder shown to be associated with:
1. Parental attitudes towards use
2. Early onset (adolescent) use
3. Route of administration
4. Regular/daily use
Take home points

- Increasing prevalence with legalization
- Risky for adolescent brain
- High rates of comorbidity
- THC, CBD, other compounds
- Intoxication, withdrawal, use disorder
- Early use, daily use → poorer outcomes
- Some medical, no psychiatric indications
- Legalization → adolescent protection? Study?
Thank You!

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