Cannabis Use Disorders: Current Perspectives

Margaret Haney, Ph.D.

Director: Marijuana Research Laboratory
Professor of Neurobiology (in Psychiatry)

Columbia University Medical Center
New York State Psychiatric Institute

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No conflicts of interest
Outline

1. Testing Medications Targeting:
   * Withdrawal and Relapse
   * Intoxication

2. Predictors of Relapse

3. Sex Differences 🫀♂️
Cannabis: Hemp Plant

- > 100 cannabinoids
- $\Delta^9$-THC primary psychoactive component: defines potency
- Scientific understanding of the effects of the remaining cannabinoids in humans is in its infancy
- Old drug, new science
Public policy changes occurring in a scientific vacuum

Conversation even among scientists can be polarized:

Miracle cure -vs- Hazard
Issues often muddied in public discussion yet are distinct

- **Legalization of recreational use:**
  Issue for **voters** to decide (ideally with an *honest* discussion of risks and benefits)

- **Legalization of medical use:**
  Should decisions about what constitutes an efficacious **medication** also be decided by **vote**? Do we vote on antibiotics?

Cannabis has escaped the process required of every other prescribed medication: randomized, placebo-controlled studies

Public policy changes re. *medical marijuana* have vastly surpassed what has been shown scientifically
Marijuana use is increasing.

Near Daily Use In Past Year / Month, ages 12 and older

2013: **4.2 million people reported cannabis abuse or dependence**
SAMHSA 2014

Approximately **6% HS seniors smoke daily**
Marijuana Potency is Increasing

Average Δ9-tetrahydrocannabinol (THC) concentration of Drug Enforcement Administration specimens by year, 1995–2014

Cannabidiol content decreased from .28% in 2001 to .15% in 2014

ElSohly et al., 2016, Biological Psychiatry
Treatment

- 24% admitted for drug treatment reported MJ as their primary drug: *steady increase over past decade*

- Subset is seeking treatment on their *own* initiative

- **WHY?** Dissatisfaction with multiple areas of functioning and concerns about future health; *unable to stop MJ use*

- Psychological and behavioral therapies work better than no treatment, but *relapse rates to MJ high*; comparable to cocaine and opiate treatment: abstinence rates 15-37%

- *A variety of treatment options are needed*

SAMHSA 2013; Copeland et al., 2001; Moore and Budney 2003, 2006; Kadden et al., 2007; MTPRG 2004
Translational bridge: preclinical and clinical studies

Active and placebo MJ and active and placebo medications tested under within-subject, inpatient controlled conditions

Measure behavior around the clock: mood, drug craving, cognitive task performance, food intake, sleep, but most importantly, MJ self-administration – which appears to best predict medication effects in the clinic
Participants

- Nontreatment seeking
- **Heavy users:** Smoke MJ 6-7 days/week (6-15 joints/day)
- No major psychiatric disorder
- May abuse but not meet dependence on other drugs except *often nicotine*
- **Double-blind:** Volunteers told MJ and capsule strength may change at any point. Do **not** know objective is to characterize withdrawal and relapse
Pharmacological Approaches

1. Decrease cannabis withdrawal and relapse to cannabis use

2. Block cannabis intoxication
Cannabis Withdrawal

- Manifests >24 hours of abstinence and lasts 1-2 weeks
- Contributes to relapse and maintenance of marijuana use

- Anxiety
- Irritability
- MJ craving
- Restlessness
- Food intake
- Sleep quality

Cannabis Withdrawal

<table>
<thead>
<tr>
<th>Table</th>
<th>Cannabis withdrawal disorder symptoms: a working proposal for DSM-5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Three or more of the following symptoms would be required for a diagnosis of cannabis withdrawal syndrome:</td>
</tr>
<tr>
<td></td>
<td>• Irritability, anger, or increased aggression</td>
</tr>
<tr>
<td></td>
<td>• Nervousness or anxiety</td>
</tr>
<tr>
<td></td>
<td>• Sleep difficulty (insomnia)</td>
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<tr>
<td></td>
<td>• Decreased appetite or weight loss</td>
</tr>
<tr>
<td></td>
<td>• Restlessness</td>
</tr>
<tr>
<td></td>
<td>• Depressed mood</td>
</tr>
<tr>
<td></td>
<td>• At least 1 of the following physical symptoms causing significant discomfort: stomach pain, shakiness/tremors, sweating, fever, chills, or headache</td>
</tr>
<tr>
<td></td>
<td>The DSM text describing this disorder would also discuss the following symptoms as having been observed in studies, with more research needed to determine their validity or significance:</td>
</tr>
<tr>
<td></td>
<td>• Disturbing/strange dreams</td>
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<tr>
<td></td>
<td>• Fatigue</td>
</tr>
<tr>
<td></td>
<td>• Yawning</td>
</tr>
<tr>
<td></td>
<td>• Difficulty in concentrating</td>
</tr>
</tbody>
</table>

- **Reliable**
- **Time-Dependent**
- **Pharmacologically Specific**
- **Clinical Significance**

*Budney et al., 2004, 2011*
Placebo-controlled Studies: Withdrawal

- **Bupropion SR** (300 mg/day) *worsened* mood during MJ withdrawal Haney et al., 2001; *negative clinical data*: Carpenter et al., 2009

- **Divalproex** (1500 mg/day) *worsened* mood during MJ withdrawal Haney et al., 2004; *negative clinical data*: Levin et al., 2004

- **Nefazodone** (450 mg/day) *decreased* anxiety and muscle pain during MJ withdrawal but no effect on irritability, misery Haney et al., 2003; *negative clinical data*, Carpenter et al., 2009

- **Dronabinol** (50 mg/day) *decreased* anxiety, misery, and MJ craving during MJ withdrawal at a dose that produced no intoxication Haney et al., 2004
Does Decreasing Withdrawal Decrease Relapse?

- Drug taking an essential behavior to target
- Developed a laboratory model of MJ relapse, defined as resumption of MJ use after a period of abstinence
- Structured conditions so that a return to MJ use by nontreatment seekers is costly: Individual puffs have to be purchased using actual study earnings

Self-administration of cocaine, cannabis and heroin in the human laboratory: benefits and pitfalls

Margaret Haney
College of Physicians and Surgeons of Columbia University and the New York State Psychiatric Institute, Department of Psychiatry, New York, USA

<table>
<thead>
<tr>
<th>Day</th>
<th>MJ Strength</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.6%:</td>
<td>Experimenter administered</td>
</tr>
<tr>
<td>2</td>
<td>0.0%:</td>
<td>Self-administration</td>
</tr>
<tr>
<td>3</td>
<td>0.0%:</td>
<td>Self-administration</td>
</tr>
<tr>
<td>4</td>
<td>0.0%:</td>
<td>Self-administration</td>
</tr>
<tr>
<td>5</td>
<td>5.6%:</td>
<td>Self-administration</td>
</tr>
<tr>
<td>6</td>
<td>5.6%:</td>
<td>Self-administration</td>
</tr>
<tr>
<td>7</td>
<td>5.6%:</td>
<td>Self-administration</td>
</tr>
<tr>
<td>8</td>
<td>5.6%:</td>
<td>Self-administration</td>
</tr>
</tbody>
</table>

- **Withdrawal**
- **Relapse**
- **Intoxication**
<table>
<thead>
<tr>
<th>Medication</th>
<th>Withdrawal Symptoms</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronabinol</td>
<td>Mood, Sleep, Appetite</td>
<td>x</td>
</tr>
<tr>
<td>Lofexidine</td>
<td>Sleep</td>
<td>↓</td>
</tr>
<tr>
<td>Dronabinol + Lofexidine</td>
<td>Mood, Sleep, Craving, Appetite</td>
<td>↓</td>
</tr>
<tr>
<td>Baclofen</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Sleep, Appetite</td>
<td>x</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Sleep, Somatic sx, Craving</td>
<td>↑</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Mood, Sleep, Craving, Appetite</td>
<td>↓</td>
</tr>
</tbody>
</table>
Nabilone vs Dronabinol

- Dronabinol has poor and variable bioavailability (4-20%) which may contribute to poor efficacy

- By comparison, nabilone, a synthetic analog of THC, has:
  1) higher bioavailability (60-90%)
  2) a longer duration of action
  3) clearer dose-linearity
  4) urinary metabolites distinct from MJ
Nabilone Decreased Mood symptoms of Withdrawal; no intoxication

*Neither nabilone dose increased ratings of capsule liking or desire to take capsules again relative to placebo*
Nabilone Decreased MJ Withdrawal: Sleep
Nabilone Decreased MJ withdrawal: Food Intake

Daily Caloric Intake

- 5.6%: 5000 kcal
- 0.0%: 5000 kcal

Body Weight

- 5.6%: 70 kg
- 0.0%: 70 kg

Eating Occasions

- 5.6%: 10 occasions
- 0.0%: 10 occasions

Number

- 5.6%: 10
- 0.0%: 10

Nabilone dose (mg/day)
Nabilone Decreased MJ Relapse
Conclusions: Nabilone

- Attenuated MJ withdrawal symptoms and relapse
- May produce mild intoxication depending on dose but no indication of abuse liability: slow onset, no liking or desire to take medication again
- Long duration of action: one dosing/day may suffice

Overall, nabilone’s ability to both attenuate MJ withdrawal and relapse support its clinical testing in patients seeking treatment for their MJ use.
Pharmacological Approaches

1. *Decrease cannabis withdrawal and relapse*

2. *Block cannabis intoxication*
Pharmacological Approaches

1. *Decrease cannabis withdrawal and relapse*

2. *Block cannabis intoxication:*
   - Naltrexone*
   - Cannabidiol
   - Pregnenalone Derivative

*Haney et al., Neuropsychopharmacology, 2016*
Oral CBD (300-600 mg) is reported to decrease oral THC (dronabinol) intoxication in some but not all studies.

Those showing CBD attenuates THC’s effects have tested one dose of CBD and one dose of dronabinol, so it is difficult to draw conclusions about the nature of this interaction.

Zhornitsky and Potvin, 2012; Crippa et al., 2004; Zuardi et al., 1993a, b, 2012; Bergamaschi et al., 2011; Bogwardt et al., 2008; Winton-Brown et al., 2011; Fusar-Poli et al., 2009; Juckel et al., 2007; Roser et al., 2008
If oral CBD attenuates cannabis’ positive subjective effects, it may have potential as a treatment medication for cannabis use disorder.

No study has directly compared the effects of a range of oral CBD doses in combination with smoked cannabis.

To determine if CBD pretreatment (0, 200, 400, 800 mg p.o., STI Pharmaceuticals UK) decreases the reinforcing, subjective, cognitive, and physiological effects of MJ (0.01, 5.30% THC) relative to placebo.
I Feel "High"

Inactive Marijuana

<table>
<thead>
<tr>
<th>CBD (mg)</th>
<th>0</th>
<th>200</th>
<th>400</th>
<th>800</th>
</tr>
</thead>
</table>

Time

mm (max = 100)
I Feel "High"

Inactive Marijuana

Active Marijuana

CBD (mg)
- 0
- 200
- 400
- 800

mm (max = 100)

Time

CBD
MJ

I Feel "High"
Desire to Smoke Cannabis

Like Cannabis

Cannabis Strength

Street Value

CBD x MJ p<0.09
Cannabis Self-administration

# Puffs purchased (max = 3)

Inactive Cannabis | Active Cannabis

CBD Dose (mg)

% Self-Administering Cannabis

Inactive Cannabis | Active Cannabis

CBD Dose (mg)

p < 0.11
Results

- Active cannabis alone produced prototypical subjective and physiological effects relative to inactive cannabis:
  - ‘high,’ ‘good effect,’ drug liking, heart rate

- CBD alone had no significant effect on any outcome measured as compared to placebo

- CBD did not significantly alter any cannabis effects
Conclusions

- Oral CBD well tolerated but did not alter smoked MJ’s effects at any dose, despite plasma CBD levels exceeding those in studies reporting an attenuation.

- CBD may have clinical potential (e.g., anti-inflammatory effects, neuropathic pain, anti-tumor), yet no controlled data convincingly demonstrate CBD’s ‘antagonism’ of THC’s effects in humans.
Future Study: Pregnenalone

- CB1 receptor stimulation increases brain PREG levels (up to 4000%)

- PREG antagonizes a wide range of behavioral and somatic effects of CB1 agonists

Inhibition by pregnenolone of:

Self-administration of WIN

THC-induced DA Release

Pregnenolone Can Protect the Brain from Cannabis Intoxication
Monique Vallée et al.
Science 343, 94 (2014);
DOI: 10.1126/science.1243985
Orthosteric Antagonist

THC

Block THC Binding to CB1

Rimonabant

CB1

Adenylate cyclase
P-ERK

MAP kinase

Allosteric Antagonist

THC

Pregnenolone

Binding pocket

Disrupt CB1 signaling

CB1

Adenylate cyclase
GTPγS

Legend:

GP

GTPγS

+ / -

cAMP
P-ERK

MAP kinase

Slide courtesy of PV Piazza
PREG is a poor medication (short half-life, rapid metabolism to other steroids, low oral bioavailability)

Aelis Farma and Piervi Piazza have developed a non-metabolizable PREG analog that attenuates a vast range of CB1 agonist effects, including self-administration in rats and monkeys

Large safety window, attenuates THC effects in preclinical models while producing none of the problems of orthosteric antagonists

**C3,17-Non-Metabolized Pregnenolone Derivatives**

**A**

**THC self-administration**

<table>
<thead>
<tr>
<th>THC injections (1 h)</th>
<th>Total number of injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>1.5</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
</tr>
</tbody>
</table>

**B**

**THC priming-induced reinstatement**

<table>
<thead>
<tr>
<th>AEF0117 (µg/kg, po)</th>
<th>Rate of responding (r/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.6</td>
</tr>
<tr>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>5</td>
<td>0.8</td>
</tr>
<tr>
<td>15</td>
<td>0.4</td>
</tr>
<tr>
<td>50</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Fig. 6.** THC self-administration and reinstatement in non-human primates (squirrel monkeys). (A) Treatment with AEF0117 (4 h before the session) dose-dependently decreases THC self-administration (4 µg/kg/injection) in squirrel monkeys under a fixed-ratio 10 reinforcement schedule (FR 10). Data are mean ± sem injections per session and responses per second (n = 4). (B) AEF0117 blocks THC priming-induced (40 µg/kg, iv) reinstatement of drug seeking. Data are mean ± sem vehicle injections per session (n = 4). *p < 0.01 as compared to AEF0117’s vehicle.
A. Cannabis Use Disorder (CUD)

1. Testing Medications Targeting:
   * Withdrawal and Relapse
   * Intoxication

2. Predictors of Relapse

3. Sex Differences
Relapse

✓ Clinical trials for cannabis use disorder show high rates of relapse: very few able to achieve abstinence
✓ What factors predict relapse?
✓ Using our laboratory model:

1. **Who** will relapse?

2. **Severity** of relapse, *i.e.*, the amount of MJ self-administered after a relapse initiated?
Factors Analyzed

- DEMOGRAPHIC
  - Age
  - Age of daily MJ use
  - Years smoking MJ regularly
  - Cigarette smoker (yes/no)
  - Alcohol drinks/week

- MJ INTOXICATION:
  - Peak ratings of “I Feel High” when active MJ administered 6x/day

- WITHDRAWAL SYMPTOMS:
  - MJ Craving: Peak
  - Mood: Mean peak ratings of “Restless, Miserable, Irritable and Anxious”
  - Sleep: Objective measures of Sleep Latency, Percent Time Asleep
    Subjective ratings of “Fell Asleep Early, Sleep Satisfaction, Woke Early

Collapsed data from *placebo medication* phase across studies; half relapsed (n=25) and half did not (n=26)
Questions

1. **What factors predict who will relapse?**

2. **What factors predict the severity of relapse (the number of MJ puffs self-administered)?**
Questions

1. **What factors predict who will relapse?**

   **Answer:** *Tobacco Cigarette-Smoking Status*

2. **What factors predict the severity of relapse (the number of MJ puffs self-administered)?**
Cigarette Smoking Predicted MJ Relapse

- 75% of participants smoked cigarettes
- Odds ratio = 19.11
  - 95% CI: 2.30, 158.95
  - Wald $\chi^2 = 7.45$, $p < 0.007$

* Note: Participants are allowed to smoke tobacco cigarettes *ad libitum* in the laboratory
Adolescents: 69% of those who smoked cigarettes relapsed to MJ 1 year later, compared to 54% of non-smokers de Dios et al., 2009

Adults: Cigarette smokers had significantly fewer MJ negative urines and fewer weeks of abstinence than ex-smokers Moore and Budney, 2001

Meta-analysis of drug treatment: smoking cessation was associated with a 25% increased likelihood of long-term (≥ 6 months) abstinence from alcohol and illicit drugs Prochaska et al., 2004; Gulliver et al., 2006
Why do cigarette smokers have an increased likelihood of relapsing to MJ?

- Close overlap in distribution of nicotinic and cannabinoid receptors \textit{Viveros et al., 2006}

- Acute nicotine pretreatment (21 mg patch) increases MJ ‘high’ \textit{Penetar et al., 2005}

- Repeatedly pairing cigarettes and MJ could result in one drug cueing use of the other \textit{Moore and Budney, 2001}
Objective and Methods

Compare MJ relapse in cigarette-smoking, daily MJ smokers when they are smoking cigarettes as usual and shortly after they have quit smoking cigarettes

- Within-subjects design
- Two inpatient phases: A Quit Phase and a Smoking-as-Usual (SAU) phase in counter-balanced order
- Quit phase (7 days prior to move-in): Contingency management procedures based on urinary cotinine and carbon monoxide measures
Tobacco cessation did not affect MJ intoxication (or MJ craving)

**Fig 1:**

<table>
<thead>
<tr>
<th></th>
<th>Ratings (mm); max = 100</th>
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<tbody>
<tr>
<td>High</td>
<td></td>
</tr>
<tr>
<td>SAU</td>
<td></td>
</tr>
<tr>
<td>Quit</td>
<td></td>
</tr>
</tbody>
</table>

Ratings (mm); max = 100
Tobacco cessation did not markedly worsen MJ withdrawal symptoms
Tobacco cessation DID NOT affect MJ relapse

>87% participants relapsed to MJ whether in the SAU or Quit phase
Conclusions: Predictors

- **Current** tobacco cigarette smoking may be a clinically important marker for increased risk of MJ relapse.

- Does not appear that recent cigarette smoking *per se* influences MJ relapse: Current cigarette smoking same as recent abstinence.

- Cigarette smoking despite mounting social prohibition in concert with daily MJ use may reflect intrinsic factors, e.g., greater impulsivity or distress intolerance, that render these individuals susceptible to relapse.
A. Cannabis Use Disorder (CUD)

1. Testing Medications Targeting:
   * Withdrawal
   * Relapse
   * Intoxication

2. Predictors of MJ Relapse

3. Sex Differences
More males use marijuana

More males seek treatment

Greater risk for CUD
11.8% men vs 5.4% women, lifetime CUD
(Stinson et al., 2006)

Telescoping effect
(Khan et al. 2013; Ehlers et al., 2010; Hernandez-Avila et al., 2004)
Are there **Sex-dependent Differences** in MJ’s **Acute Subjective Effects**?

✓ Healthy, non-treatment seeking marijuana smokers

MATCHED FOR CURRENT MJ USE
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Men (N = 35)</th>
<th>Women (N = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old)</td>
<td>27 ± 5</td>
<td>27 ± 6</td>
</tr>
<tr>
<td>Race (B/W/M)</td>
<td>28 / 6 / 1</td>
<td>21 / 8 / 6</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>72.3 ± 8.7*</td>
<td>65.4 ± 15.7</td>
</tr>
<tr>
<td>CANNABIS USE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days/Wk</td>
<td>6.9 ± 0.4</td>
<td>6.8 ± 0.5</td>
</tr>
<tr>
<td>Cannabis Cigarettes/Day</td>
<td>4.9 ± 2.9</td>
<td>6.3 ± 5.6</td>
</tr>
<tr>
<td>$/Wk</td>
<td>68.8 ± 68.2</td>
<td>62.3 ± 47.3</td>
</tr>
</tbody>
</table>
Positive Subjective Drug Effects

Cooper et al., 2014

Diagram: Time (min) vs. Rating (mm) for different groups:
- Female, Inactive MJ
- Male, Inactive MJ
- Female, Active MJ
- Male, Active MJ

Legend:
- □ Female, Inactive MJ
- ○ Male, Inactive MJ
- ■ Female, Active MJ
- ● Male, Active MJ

Graph shows trends and variability over time.
Positive Subjective Drug Effects

Cooper et al., 2014

Female, Inactive MJ
Male, Inactive MJ
Female, Active MJ
Male, Active MJ
Positive Subjective Drug Effects

Cooper et al., 2014
Conclusions: Sex Differences in Abuse Liability

- Females report greater subjective effects for measures associated with increased drug taking
- Consistent with preclinical findings
- Contributes to telescoping effect?
CUD: Overall Summary

✓ Medication targets for:

Withdrawal, Relapse: Nabilone most promising
Intoxication, reinforcement: Naltrexone most promising

✓ Cigarette smoking is a clinical marker for a greater risk of MJ relapse

✓ Sex Differences: Cannabis may have higher abuse liability for women than for men
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NIDA