Cannabis, cognition, and gender: Novel treatment targets for cannabis use disorder.

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Disclosures

- No conflicts of interest to declare.
I. Background: Cannabis use and gender in the United States
II. Motivation and gender in cannabis treatment
III. Cognitive bias modification
IV. Ovarian hormones
V. Future directions
I: Background

Substance Use Disorder (SUD) treatment development research

- Sex/gender factors
- Cognitive mechanisms
• Cannabis Access Laws: 46 states plus DC
• Medical Use: 33 states plus DC
• Recreational Use: 10 states plus DC
• 97.7% US pop. any access laws
• 24.5% US pop. recreational access laws
Percentage of U.S. 12 Grade Students Reporting Daily Marijuana Use vs. Perceived Risk of Regular Marijuana Use

Source: The Monitoring the Future study, the University of Michigan

(Johnson et al., 2015)
1. Challenges in Cannabis Research

1) Changing social norms

2) Measurement/study design

3) Still illegal

U.S. public opinion on legalizing marijuana, 1969-2018

Do you think the use of marijuana should be made legal, or not? (%)

Marijuana Use

PAST MONTH, 2015 - 2017, 12+

See figure 13 in the 2017 NSDUH Report for additional information.

+ Difference between this estimate and the 2017 estimate is statistically significant at the .05 level.
Marijuana Use among Young Adults: Significant Increases in Women

PAST MONTH, 2015 - 2017, 18 - 25

Special analysis of the 2017 NSDUH Report.

+ Difference between this estimate and the 2017 estimate is statistically significant at the .05 level.
Marijuana Use among Women by Pregnancy Status

PAST MONTH, 2015 - 2017, 15 - 44

<table>
<thead>
<tr>
<th></th>
<th>Pregnant</th>
<th>Not Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2015</strong></td>
<td>78k</td>
<td>3.4%</td>
</tr>
<tr>
<td><strong>2016</strong></td>
<td>111k</td>
<td>4.9%</td>
</tr>
<tr>
<td><strong>2017</strong></td>
<td>161k</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

**Pregnant**

- 2015: 3.4%
- 2016: 4.9%
- 2017: 7.1%

**Not Pregnant**

- 2015: 10.3M
- 2016: 6.7M
- 2017: 12.2M

Special analysis of the 2017 NSDUH Report.

+ Difference between this estimate and the 2017 estimate is statistically significant at the .05 level.
Daily or Almost Daily Marijuana Use among Women by Pregnancy Status

PAST YEAR, 2015 - 2017, 15 - 44

PREGNANT

- 2015: 28k, 1.2%
- 2016: 60k, 2.6%
- 2017: 69k, 3.1%

NOT PREGNANT

- 2015: 1.6M, 2.7%
- 2016: 1.7M, 2.8%
- 2017: 2.1M, 3.4%

Special analysis of the 2017 NSDUH Report.

+ Difference between this estimate and the 2017 estimate is statistically significant at the .05 level.
Cannabis Use and Gender

Telescoping effect
More severe and impairing withdrawal
Greater abuse-related effects (clinical and preclinical)
Comorbid anxiety disorders
Lifetime psychiatric disorder
More severe chronic pain
Poorer quality of life

Earlier onset
Greater likelihood of lifetime CUD
Longer time to remission
Comorbid SUD

I: CUD and Cannabis Use Consequences

- Conversion rates, CUD:
  - 9% who ever use;
  - 16% who begin in adolescence
  - 25-50% of daily users

- Negative consequences:
  - psychotic disorders
  - acute cognitive impairment (working memory, processing speed, abstract reasoning).
  - altered brain development
  - impaired motor coordination
  - sx of bronchitis
  - lower educational attainment and life satisfaction

(Crane et al., 2013; Fergusson & Boden, 2008; Hall & Degenhardt, 2009; Hasin et al., 2015; Lopez-Quintero et al., 2011; Patton et al., 2002; Radhakrishnan et al., 2014; SAHMSA 2018; Volkow et al., 2014)
I. Treatment for CUD

- Approximately 1,000,000 people received treatment in 2013 (SAMHSA, 2014)
- Treatments generally show modest outcomes:
  - Psychosocial treatments (MET/CBT/CM) show best results (Budney et al. 2007; Sherman & McRae-Clark, 2016)
  - No approved pharmacotherapy to date
- Evidence suggests women show worse cannabis treatment outcomes than men (McRae-Clark et al. 2015)
- Need for novel behavioral and pharmacological treatments, particularly among vulnerable populations

Mechanisms of interest:
1. Motivation, self-efficacy
2. Cognitive processing
3. Ovarian hormones
Part II: Cannabis, motivation, and gender
Secondary data analysis

- **Aim**: Identify mechanisms that help explain gender differences in cannabis treatment outcomes.
  1. Motivation to change
  2. Self-efficacy

- **Primary Outcomes**:
  1. Point prevalence abstinence
  2. Creatinine adjusted cannabinoid levels
Methods

- 12-week, randomized, placebo-controlled clinical trial
- 18-65 y/o, cannabis-dependence, recruited 2009-2014 (N=175)
  - M age 24.0
  - 76.6% male
  - 64% Caucasian
- Baseline measures of motivation to change and self-efficacy
  - SOCRATES (Miller & Tonigan 1996): Ambivalence, Recognition, Taking Steps
  - SEQ (Stephens et al. 1993): Total self-efficacy score
- Additional clinical correlates (e.g. readiness to change, marijuana-related problems)
Results

Figure 1: Point prevalence abstinence by gender and SOCRATES-Taking Steps

→ Greater ‘taking steps’ predicted lower abstinence rates among women.

Figure 2: Creatinine adjusted cannabinoid levels by gender and Readiness to Change

→ Greater ‘readiness to change’ predicted higher cannabinoid levels among women.
Exploratory analyses: What is associated with taking steps towards change?

Women

- MJ-related problems
  - (B = 0.76; p = 0.04)

Men

- Self-efficacy
  - (B = 1.66; p = 0.006)
- Quantity of use (g)
  - (B = 0.82; p = 0.000)
Discussion

- **Person-Centered Factors**
  - Intrinsic vs. extrinsic motivation
  - Stigma, social desirability, and self-image
  - More complex presentation

- **Treatment-Centered Factors**
  - Male-dominated treatment models
  - Women’s Recovery Group (Greenfield et al)
Part III: Cannabis and Cognition

- Implicit cognition
- Cognitive bias modification
Endocannabinoid system (eCB)

- Critical role in homeostasis, neurodevelopment and cognition (neurogenesis, synaptic pruning), esp. during critical stages of cortical development (e.g. adolescence)

- CB1, CB2 receptors

- Exogenous cannabinoid exposure can disrupt these processes

Cannabis sativa

- > 100 phytochemicals

- THC → strong affinity for CB1

- CBD → may be neuroprotective

Bloom, A.S., 2004
Part III: Cannabis and Cognition

1. Structural and functional brain changes
   - Bidirectional changes in GMV (↑ cerebellum, striatum; ↓ hippocampus)
   - Decreased white matter tract integrity (prefrontal, limbic, parietal, cerebellar)
   - Activation of mesolimbic reward circuitry, decreased activation frontal regions during cue task

2. Neurocognition
   - Acute deficits in verbal learning, working memory, executive function, processing speed; some evidence on long-term neurocognitive decline (decrease in IQ score over time)
   - Evidence suggests reversal of cognitive deficits within 4-6 weeks of abstinence

3. Mixed findings: must consider age of onset, freq/quantity, cannabis composition (THC:CBD)

see Crane et al., 2013; Curran et al., 2016; Sagar & Gruber, 2018 for recent reviews
Part III: Cannabis and Cognition

- **Sex/gender Differences**
  - Neurodevelopment occurs earlier in females compared to males
  - Females show greater CB1 desensitization to THC
  - Males have greater CB1 density
  - Evidence on gender differences in cannabis-related neurocognitive function is equivocal (rigorous gender studies are limited)
    - Acute vs. non-acute effects
    - Samples differ on severity, chronicity
    - Cannabis composition never considered until recently

- Gender differences in neural activity in response to subliminal cannabis cues (Wetherill et al., 2015)
Cognitive targets in CUD treatment

- Dual process model of addiction
  - Implicit processes: automatic, reward-driven, contingency-based learning
  - Explicit processes: reflective, inhibitory, executive-control related

- Cannabis implicated in dysfunction of both
- Treatments may target *top-down* or *bottom-up* processing

see Crane et al., 2013; Curran et al., 2016; Sagar & Gruber, 2018 for recent reviews
Cognitive Bias

Implicit motivational processes

- Cognitive bias
- Incentive-sensitization theory (Robinson & Berridge, 1993)
- Attentional bias, Approach bias

1. Cognitive bias modification (retraining)
2. Cognitive bias as a moderator
Cannabis and Cognitive Bias

Approach Bias: the action tendency for approach behavior following exposure to highly salient drug cues, which may occur outside an individual’s awareness.

- Alcohol, opioids, nicotine, cannabis

Cannabis Approach Bias
- Activation of mesolimbic reward pathway, reduced activation of executive control-related regions
- Increased use, greater problem severity at 3 year follow-up
- Women may be more responsive to cognitive bias retraining (i.e. subliminal priming study)

Democritus (460–370 BCE)
- "Pleasure and pain are the criterions of decisions on what needs to be avoided or striven to.
- "

William James
- Principles of Psychology (1890)

(Wetherill et al. 2015)

Neumann RJ, Strack F.

Approach and avoidance: the influence of proprioceptive and exteroceptive cues on encoding of affective information.


(Cousijn et al, 2012; 2013; Wetherill et al. 2015)
Cognitive Bias Modification

- **Approach Bias Modification (ABM):** Computerized intervention seeks to retrain implicit biases to avoid, rather than approach, drug-related stimuli.

- **Approach-Avoidance Task (AAT)** Wiers and colleagues (2009; 2010)
  - Reduced alcohol relapse rates (10-13%) at 1 year (Eberl et al 2013)
  - Decreased neural activity in mesolimbic region and reduced craving (Wiers et al. 2015)
  - Reduced cigarette consumption and dependence severity (Wittekind et al 2015)
  - No clinical trials for cannabis; no investigation of gender differences
Pilot Study (P50 SCOR)

**Objective:** To inform the development of novel behavioral treatments for CUD. Evaluate the feasibility and preliminary efficacy of ABM in cannabis using adults.

- **Specific Aims:**
  1. Aim 1: Does ABM reduce cannabis approach bias?
  2. Aim 2: Does ABM reduce cannabis cue reactivity?
  3. Aim 3: Does gender moderates these effects?

- **Exploratory Aim:** Examine the effect of ABM on cannabis use outcomes.
Materials and Methods

- **Design**: Randomized, sham-controlled study of ABM on cannabis cue-reactivity and use
- **Sample**: Non-treatment-seeking adults age 18-65, moderate-severe DSM-5 CUD
- **Intervention**: 4-session Marijuana Approach Avoidance Task (M-AAT)
- **Outcomes**:
  - MJ approach bias
  - Cue-reactivity (subjective, physiological)
  - Cannabis use
Marijuana Approach-Avoidance Task

- Reaction time task
- Push/pull joystick in response to irrelevant stimulus feature (i.e. border color)
- Zooming feature to simulate approach (pull)/avoidance (push)

Randomized to Active training (experimental) or Sham training (control)

Approach bias score = (Push MJ_RT – Pull MJ_RT). Positive number → greater approach bias
M-AAT
M-AAT

- Pre-assessment (2 blocks, 96 trials each, picture set A)
- 4 training sessions (2 blocks, 192 trials each, picture set A)
- Post-assessment (2 blocks, 96 trials each, picture set B)
- Follow-up assessment (2 blocks, 96 trials each, picture set B)

**Sham training**

- Mj: 50%
- Non-Mj: 50%

**Active training**

- Mj: 90%
- Non-Mj: 10%
Cue reactivity

- Live cue exposure: visual, tactile, auditory, olfactory
- Outcome: physiological reactivity (BP, HR), subjective reactivity (craving)
Study Timeline

**Week 1**
- **Baseline**
  - MINI
  - TLFB
  - UDS
- **Visit 1**
  - Cue reactivity
  - App Bias Pre-Assessment
  - MAAT training session 1
- **Visit 2**
  - MAAT training session 2

**Week 2**
- **Visit 3**
  - MAAT training session 3
- **Visit 4**
  - MAAT training session 4
  - App bias post-assessment
  - Cue-reactivity

**2-week F/u**
- App bias f/u assessment
- Cue-reactivity
Results

- Completers (N = 33)
  - 58% female
  - $M(SD)$ age 24.3(5.8)
  - 85% white
  - 57% some college

- Baseline cigarette, alcohol, or cannabis use did not differ by condition or sex
Results – Specific Aim 1: MJ Approach Bias

**Note**: Data show raw approach bias scores across condition, valence (cue type), and visit. Results indicate overall cannabis approach bias, compared to neutral cue bias, across groups at baseline. Three-way interaction Condition x Valence x Visit was not significant.
Specific Aim 2: Cue-reactivity

*Adjusting for baseline cue-induced craving, participants receiving ABM (n=16) demonstrated blunted craving response at the end of treatment compared to controls (n=16), though not at follow-up. No gender effect on cue-reactivity.

* p=0.05

** p=0.011

*Figure 1a. Visit 4 cannabis craving by valence.*

*Figure 1b. Follow-up cannabis craving by valence.*
Exploratory Aim: Cannabis use outcomes

Adjusting for baseline, men receiving ABM (n=7) had fewer MJ use sessions per day following treatment than women in the active group (n=9); this difference was not significant in the sham group.
Summary

1. No treatment effect of ABM on cannabis approach bias.
2. Blunted cue-reactivity in treatment group at end-of-study.
3. Men reported fewer sessions/day at end of study compared to women.

Limitations:
1. Sample size – replication is needed in fully-powered sample (K23)
2. Non-treatment seeking (i.e. unmotivated)
3. Ongoing use may undermine efficacy
IV. Ovarian Hormones and Substance Use

Sex and menstrual cycle differences in the subjective effects from smoked cocaine in humans.

Sofu

Increasing progesterone levels are associated with smoking abstinence among free-cycling women smokers who receive brief pharmacotherapy.

Saladin ME

Addiction

RESEARCH REPORT

Menstrual phase effects on smoking relapse

Progestosterone for the reduction of cocaine use in post-partum women with a cocaine use disorder: a randomised, double-blind, placebo-controlled, pilot study

Lancet Psychiatry 2014; 1: 360-67

Kimberly Ann Yonkers, Ariadna Forray, Charla Nich, Kathleen M Carroll, Cristine Hine, Brian C Merry, Howard Shaw, Julia Shaw, Mehmet Sofuoglu
Specific aim 1: Investigate the feasibility of exogenous progesterone administration for cannabis withdrawal in women.

- Medication adherence; Progesterone levels

Specific aim 2: Examine the efficacy of exogenous progesterone on cannabis withdrawal in women.

- Self-reported withdrawal sx; Urine cannabinoid levels

Exploratory aim: Examine the effect of progesterone on cognitive functioning during cannabis withdrawal.
Study Design

Menstrual Tracking Phase

Consent & Eligibility Assessment

Begin abstinence (a.m.)

Study Day 1 Lab visit

Start medication (p.m.)

Study Days 2 – 4 Home-based procedures

Twice daily medication (a.m./p.m.)

Study Day 5 Lab visit

Last med dose (a.m.)

Daily assessments: hormone sample, saliva drug test, cannabis withdrawal

Fig. 1. Study design and timeline.
Procedures:
- EMA surveys through Redcap
- Tele-medications adherence
- Tele-drug testing
- Salivary hormone samples
### Results

<table>
<thead>
<tr>
<th></th>
<th>Full Sample</th>
<th>PROG</th>
<th>PBO</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 8)</td>
<td>(n = 3)</td>
<td>(n = 5)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong> M (SD)</td>
<td>22.2 (2.6)</td>
<td>21.7 (1.5)</td>
<td>22.6 (3.3)</td>
<td>0.667</td>
</tr>
<tr>
<td><strong>Race</strong> N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>2 (25)</td>
<td>2 (66.7)</td>
<td>0 (0)</td>
<td>0.049</td>
</tr>
<tr>
<td>Caucasian</td>
<td>6 (75)</td>
<td>1 (33.3)</td>
<td>5 (100)</td>
<td></td>
</tr>
<tr>
<td><strong>Education</strong> N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>6 (75)</td>
<td>3 (100)</td>
<td>3 (60.0)</td>
<td>0.237</td>
</tr>
<tr>
<td>College degree</td>
<td>2 (25)</td>
<td>0 (0)</td>
<td>2 (40.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Cannabis sessions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per day (30 day TLFB) M (SD)</td>
<td>1.72 (0.92)</td>
<td>1.73 (0.68)</td>
<td>1.72 (1.11)</td>
<td>0.986</td>
</tr>
<tr>
<td><strong>Cannabis use days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(past 30) M(SD)</td>
<td>27.5 (5.15)</td>
<td>30.0 (0.00)</td>
<td>26.3 (6.25)</td>
<td>0.324</td>
</tr>
<tr>
<td><strong>Standard drinks</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>per day (30 day TLFB) M (SD)</td>
<td>0.71 (0.73)</td>
<td>0.63 (0.80)</td>
<td>0.75 (0.77)</td>
<td>0.841</td>
</tr>
</tbody>
</table>

*Note: PROG = progesterone condition, PBO = placebo condition.*
Results
Aim 1: Feasibility

1. Medication adherence and tolerability
   i. Self-report: 88% ITT sample, 100% among completers
   ii. Video capture: 87.5% ITT; 98% completers (1 video upload error)

2. Progesterone levels

Fig. 2. Progesterone levels (pg/ml) by treatment condition and time.

Note: The treatment x time interaction (F = 3.50, p = 0.027) demonstrates increased progesterone levels among participants receiving exogenous progesterone (n=3) compared to placebo (n=5).
Results
Aim 2: Cannabis Abstinence and Withdrawal

Cannabis abstinence

1. 100% (40/40) saliva samples were THC negative

2. Urine cannabinoids decreased 56% from Day 1 to Day 5, (582.21 ng/ml → 258.07 ng/ml; p = 0.06)

3. Self-reported abstinence 100%

4. Groups did not differ (p = 0.36)
Results
Aim 2: Cannabis Abstinence and Withdrawal

Cannabis withdrawal

CWS Total Score
(Treatment x Time; p = 0.38)

Placebo  Progesterone

CWS - Craving
(Treatment x Time; p=0.07)

Placebo  Progesterone
Summary

1. Feasibility of combined human lab and home-based procedures using EMA: A model for future pharmacotherapy trials?

2. Exogenous progesterone shows potential for treating cannabis withdrawal in women

Limitations:

 Sample size
 Longer duration to assess withdrawal (peaks 2-6 days, can last up to 14)
 Variable dosing (100mg, 200mg, 400mg)
Future directions

1. Cognition: Dual process models
   a) K23 (PI Sherman): Cognitive bias modification for CUD.
      
      Can we attenuate implicit reward driven processes while enhancing top-down control-related processes?
   b) Cognitive enhancement paradigms targeting other domains of fx (e.g. working memory, inhibitory control)

2. Ovarian Hormones
   a) U54 SCORE (McRae-Clark) Progesterone for cannabis withdrawal and stress reactivity
      
      Does progesterone reduce stress-reactivity (i.e. stress, drug craving) in females with CUD, compared to males?
      
      Does baseline cognitive functioning (cognitive bias) moderate treatment effect?
      
      Does progesterone improve cognitive functioning in the context of abstinence?
1. Component 1: “Impact of progesterone on stress reactivity and cannabis use”

- **Assessment**
  - Informed consent
  - Inclusion/exclusion
  - Baseline measures

- **Days 1-7**
  - Progesterone or placebo
  - CREMA evaluation during cannabis abstinence
  - Daily salivary progesterone measurement

- **Day 8**
  - Laboratory evaluation of stress reactivity (TSST)
  - +
  - **Days 8-22**
  - CREMA evaluation of predictors of return to cannabis use
  - Daily salivary progesterone measurement
I would feel more in control of things RIGHT NOW if I could smoke marijuana.
Overall Summary

1. Gender differences in cannabis use patterns and corollaries of use
   i. These corollaries, combined with male-dominated models may reduce treatment efficacy in women

2. Cognitive bias modification is a novel behavioral strategy
   i. Jury is still out: Need fully-powered clinical trials w/ treatment-seekers

3. Ovarian hormones are an important mechanism in addiction, and progesterone is especially promising for the treatment of women with SUDs
   i. Reduced cannabis craving and (hopefully) stress-induced relapse in women

4. Capitalize on multi-modal methodology
   i. Maximize real-time data collection, minimize participant burden
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Thank you for your attention!

Questions??

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