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

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Disclosures

- No conflicts of interest to declare.

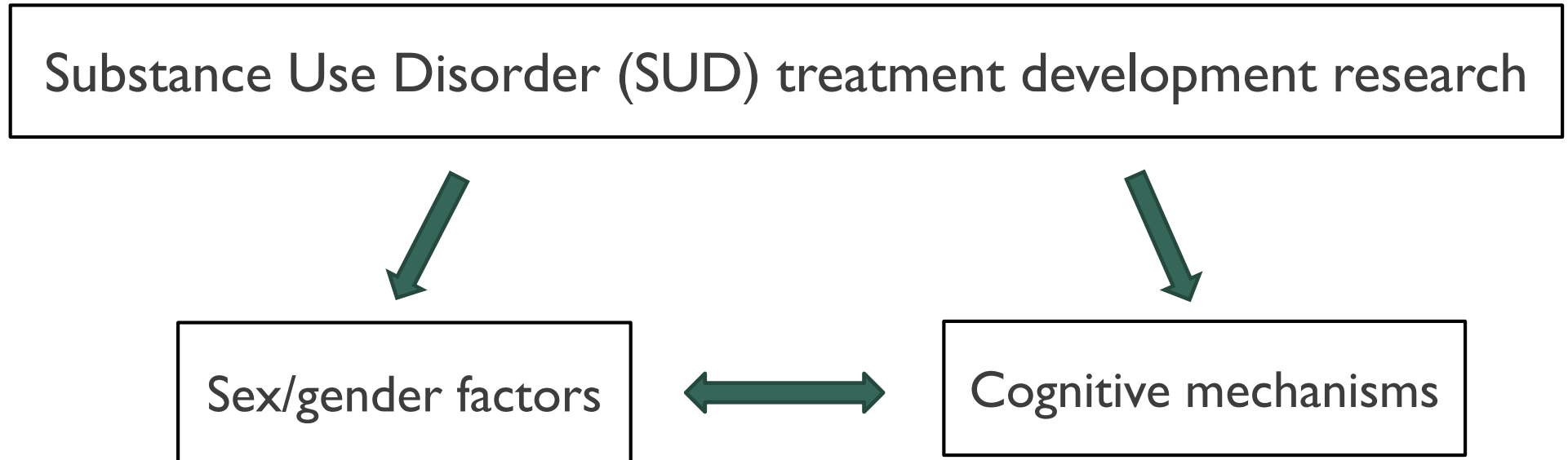


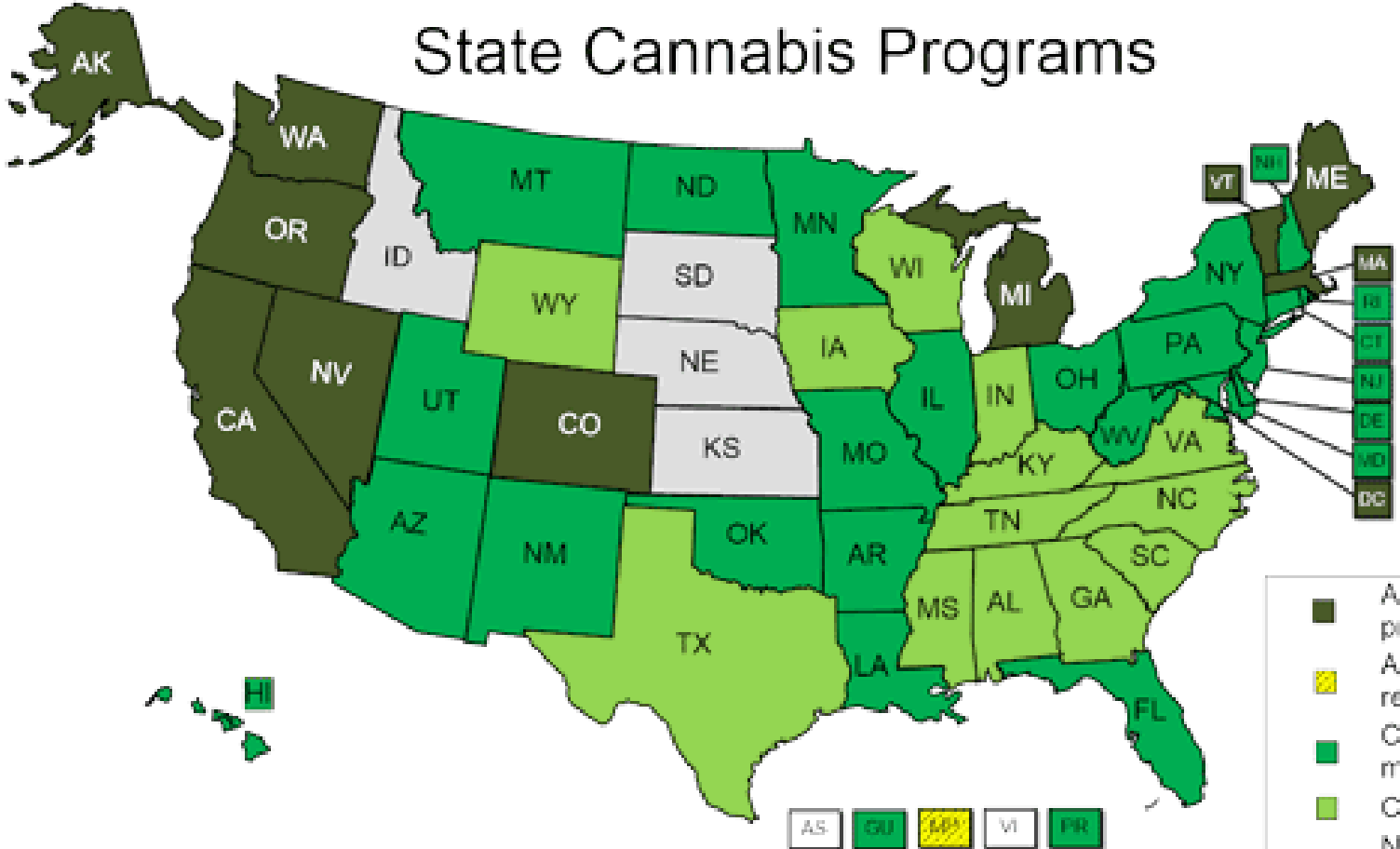
Outline

- 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

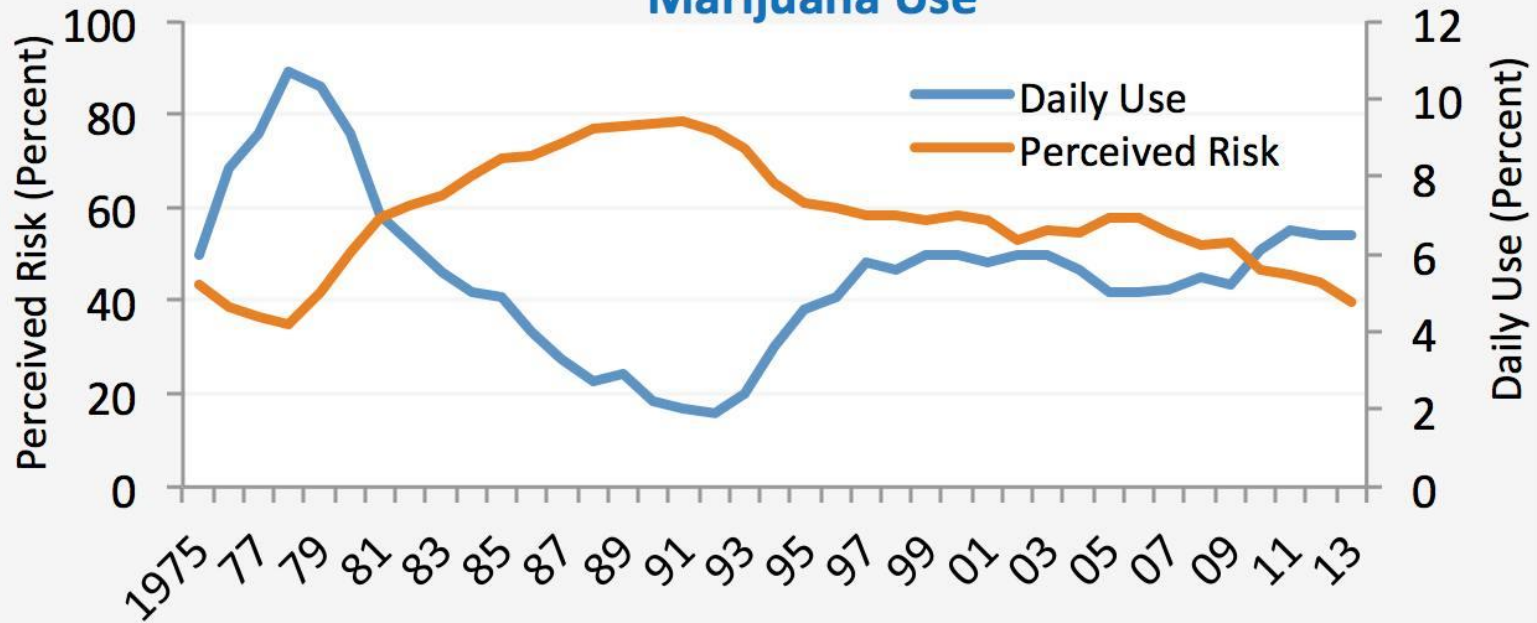




- Cannabis Access Laws: 46 states plus DC
 - Medical Use: 33 states plus DC
 - Recreational Use: 10 states plus DC
- 97.7% US pop. any access laws
 - 24.5% US pop. recreational access laws

Vermont adult use law signed Jan. 22, 2018. Effective July 1, 2018
 Limited adult possession and growing allowed, no regulated production or sales. DC, VT

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



I. Challenges in Cannabis Research

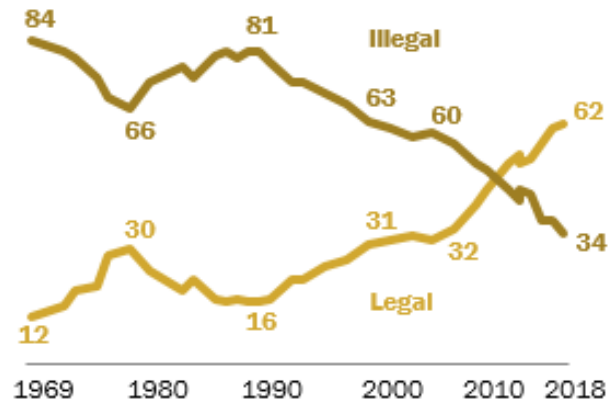
1) Changing social norms

2) Measurement/study design

3) Still illegal

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

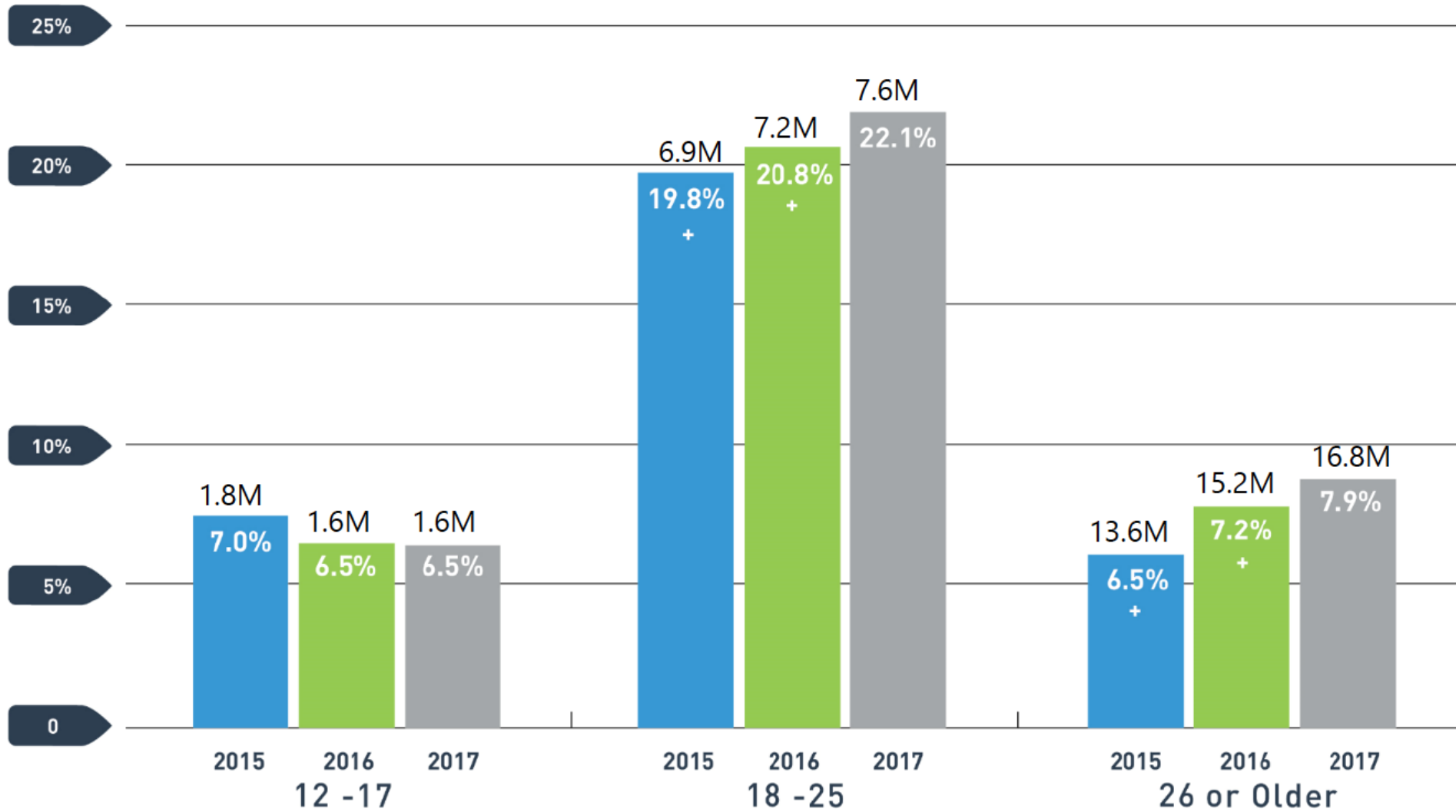
Do you think the use of marijuana should be made legal, or not? (%)



DEA

Marijuana Use

PAST MONTH, 2015 - 2017, 12+

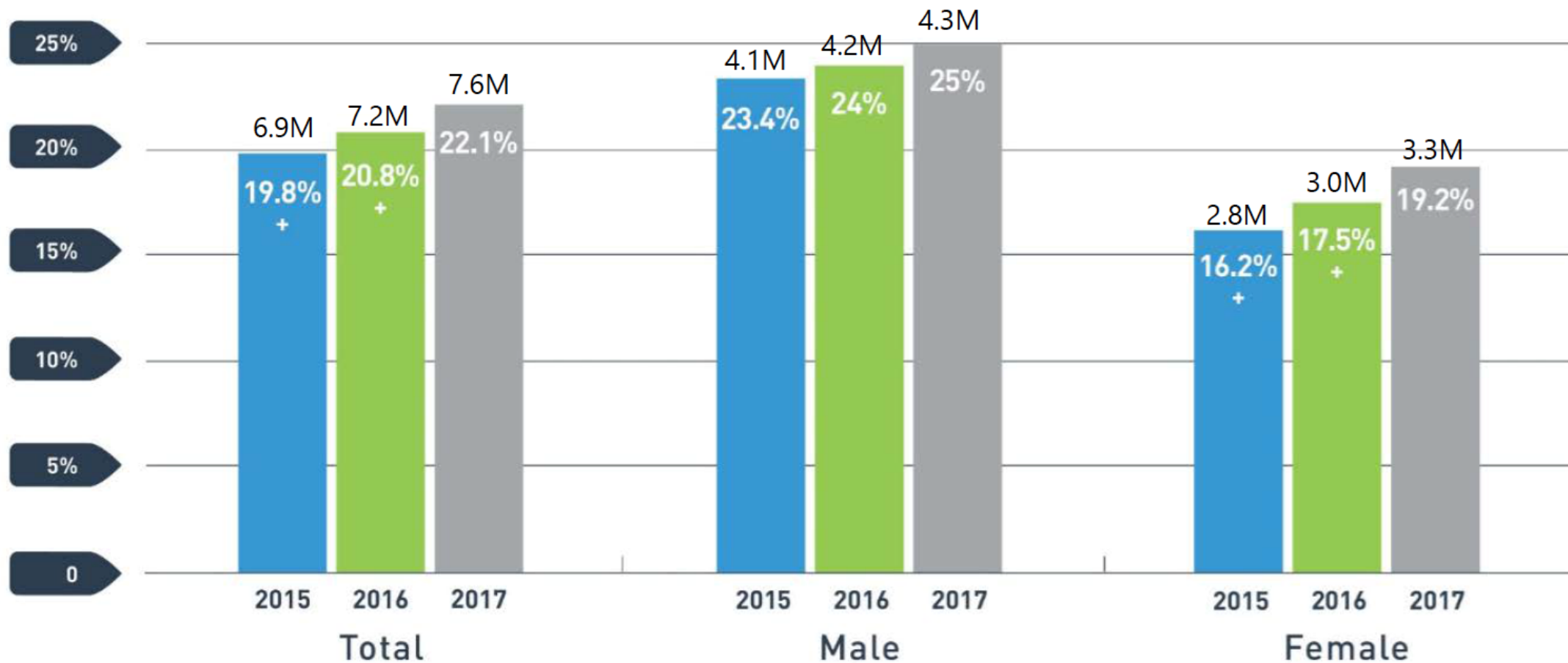


See figure 13 in the 2017 NSDUH Report for additional information.

+ 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

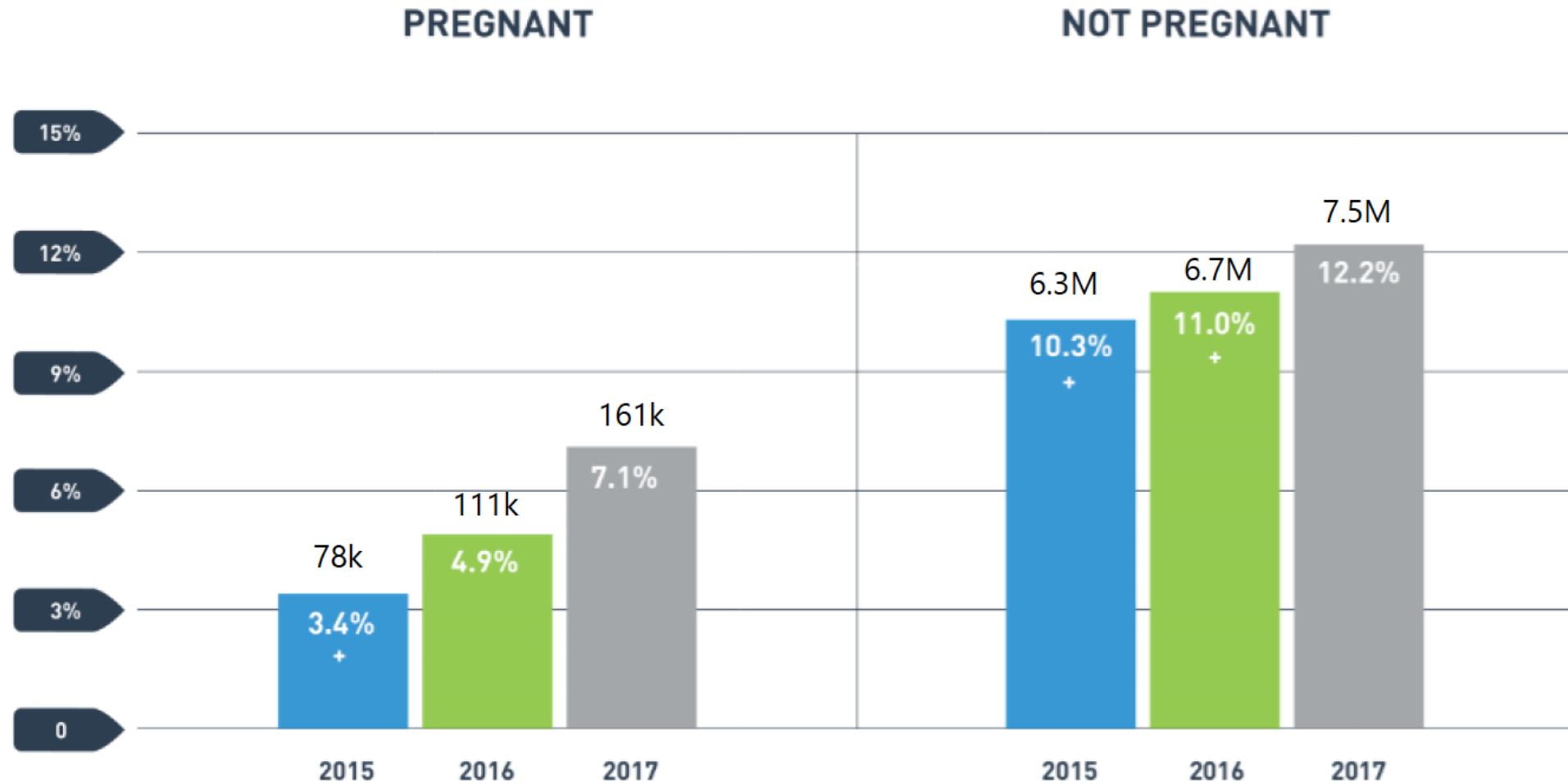


Special analysis of the 2017 NSDUH Report.

+ 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

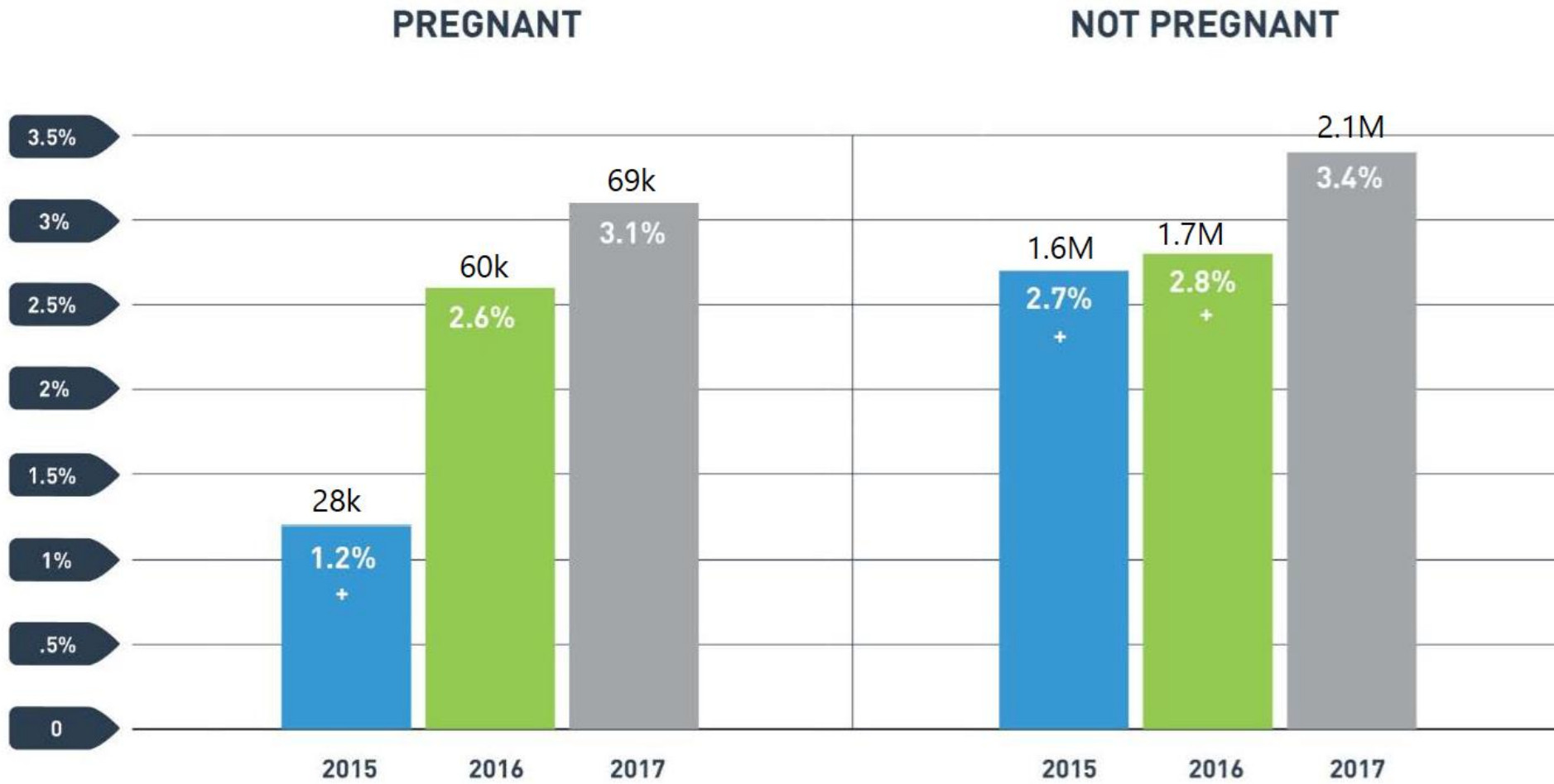


Special analysis of the 2017 NSDUH Report.

+ 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

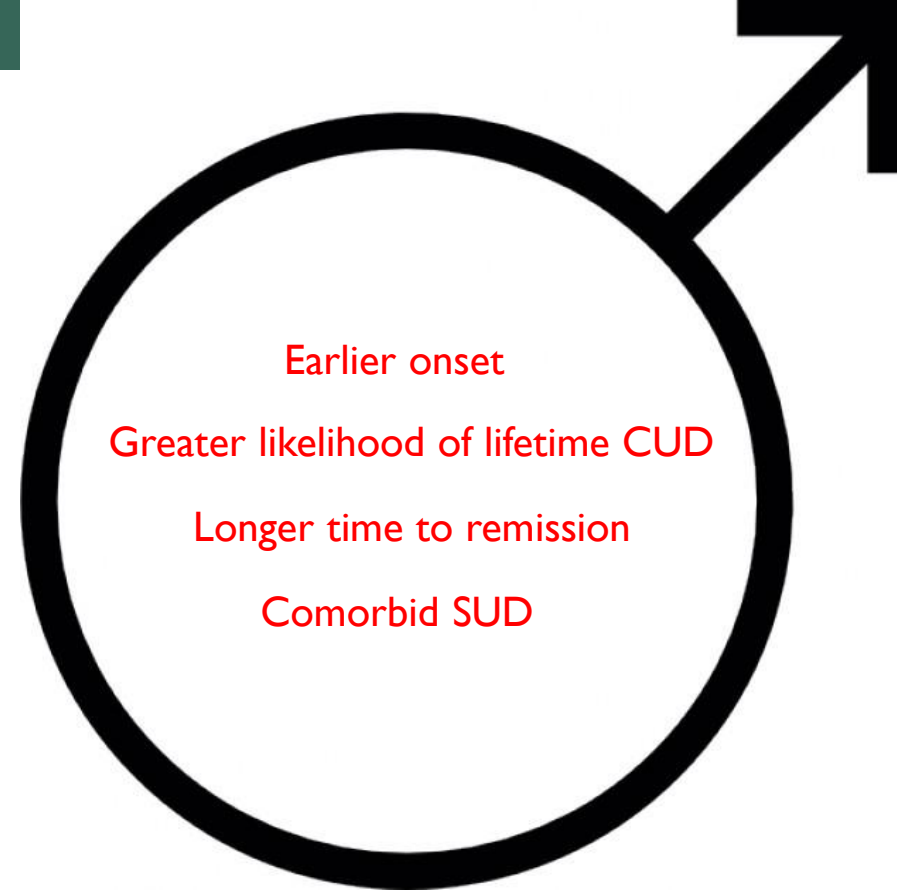
PAST YEAR, 2015 - 2017, 15 - 44



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



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's of bronchitis
 - lower educational attainment and life satisfaction



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



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdp



Buspirone treatment of cannabis dependence: A randomized, placebo-controlled trial

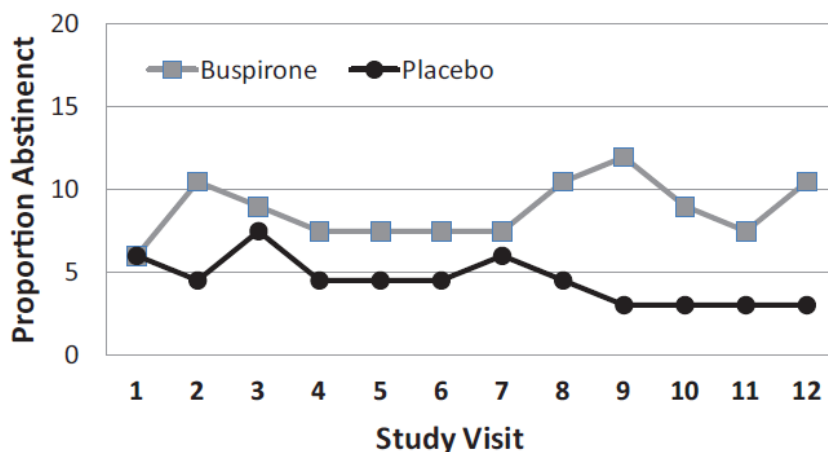


Aimee L. McRae-Clark^{a,*}, Nathaniel L. Baker^b, Kevin M. Gray^a, Therese K. Killeen^a, Amanda M. Wagner^a, Kathleen T. Brady^a, C. Lindsay DeVane^a, Jessica Norton^a

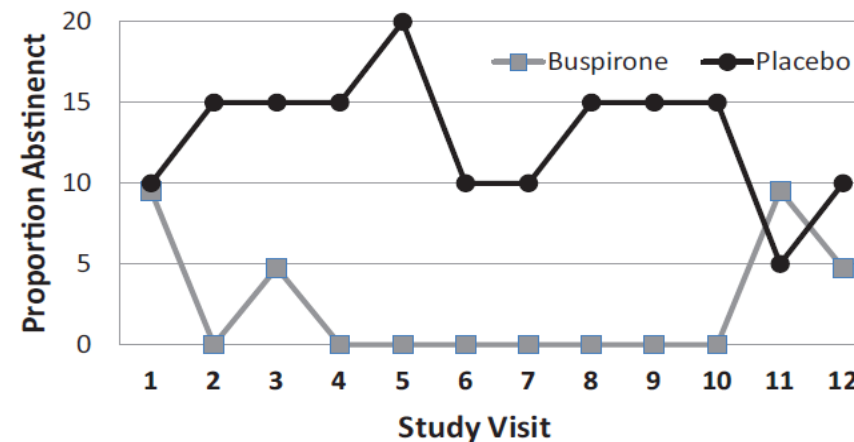
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^b Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC 29425, USA

B) Male Participants



C) Female Participants



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



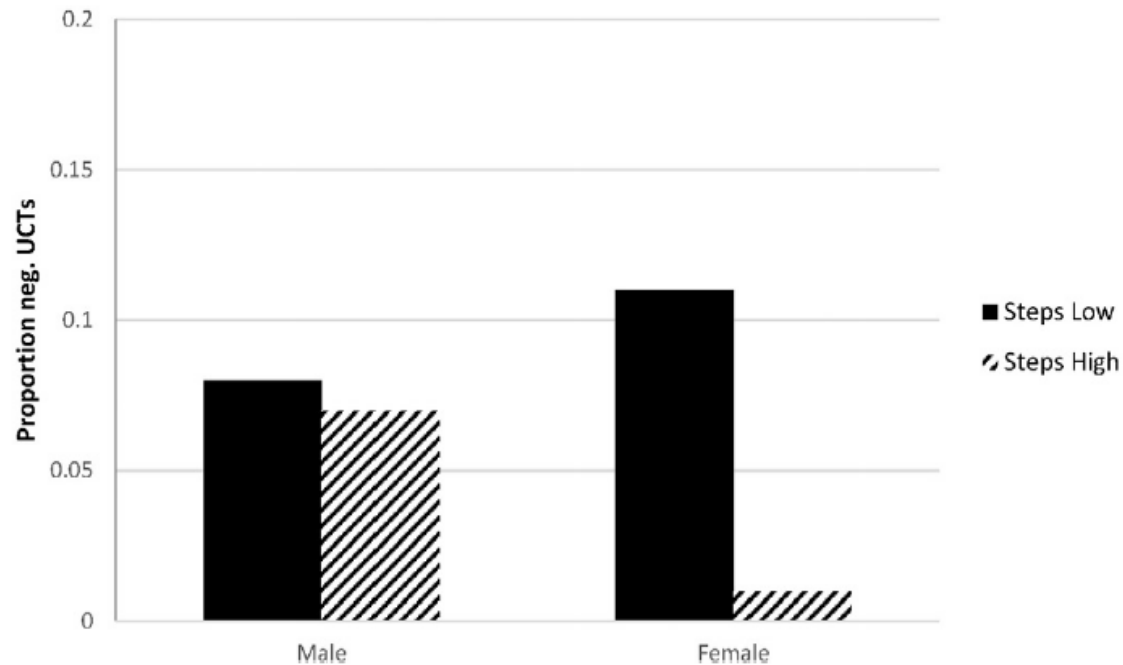
Methods

- 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)



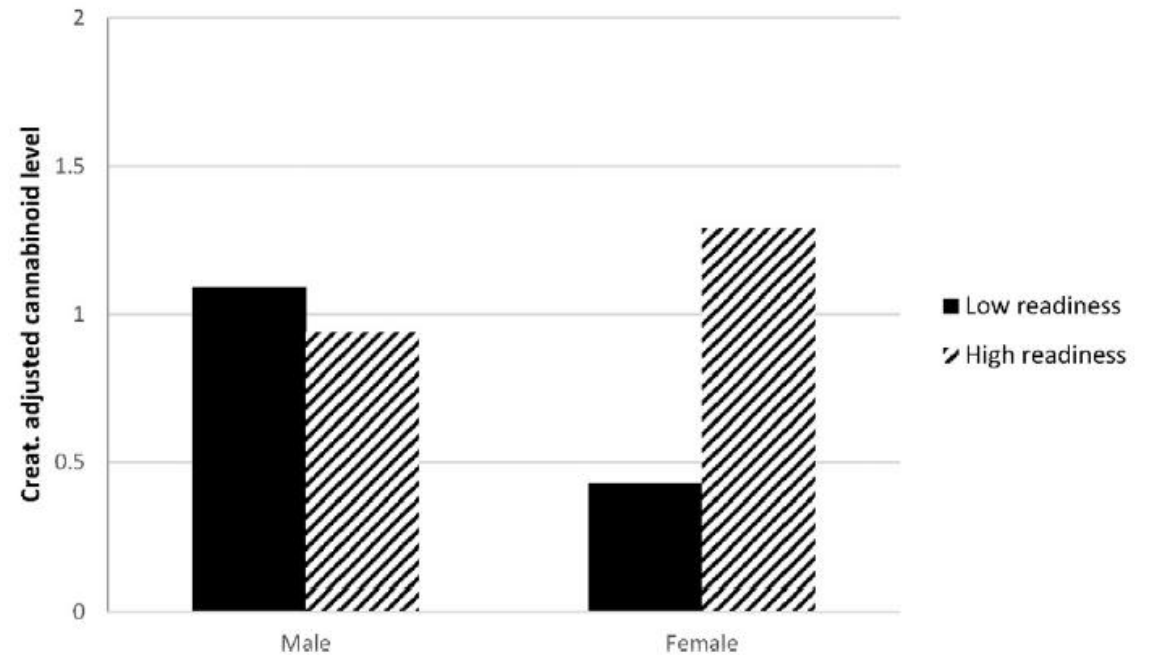
Results

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

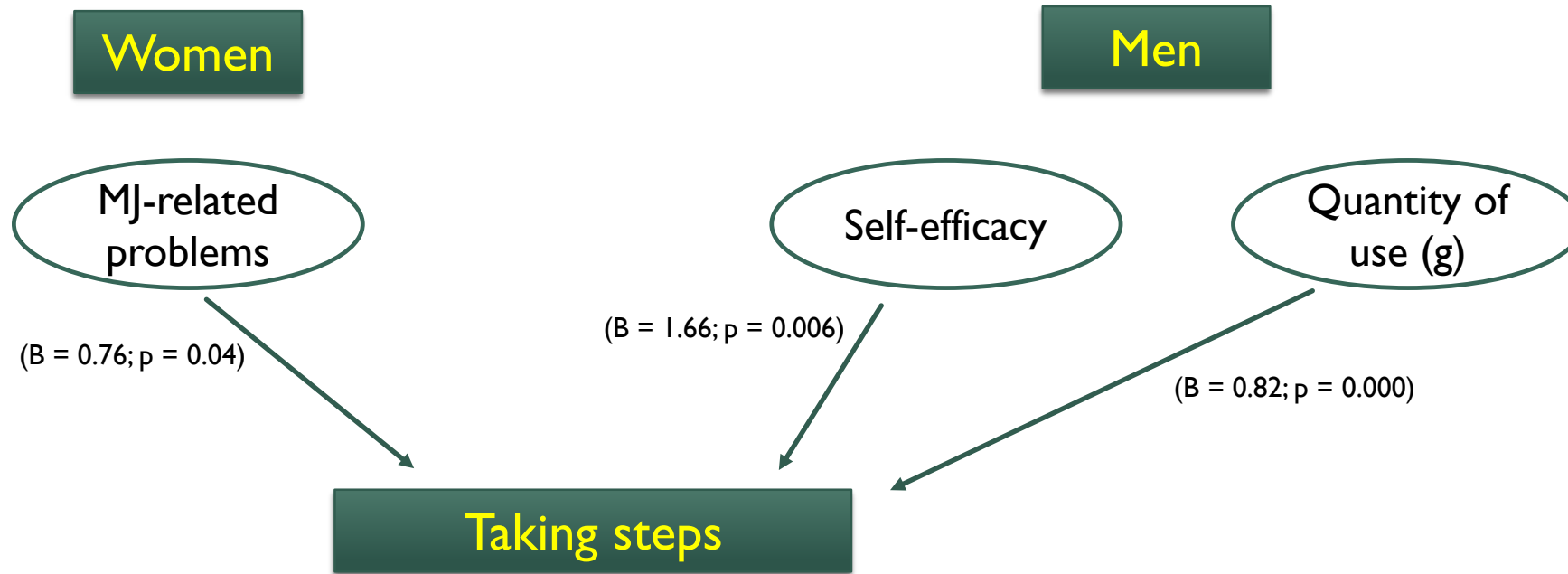


→ Greater 'readiness to change' predicted *higher* cannabinoid levels among women.



Results

Exploratory analyses: What is associated with taking steps towards change?



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 for brain development and cognitive function esp. during early development
- CBI, CBN
- Exogenous cannabinoids like these produce effects

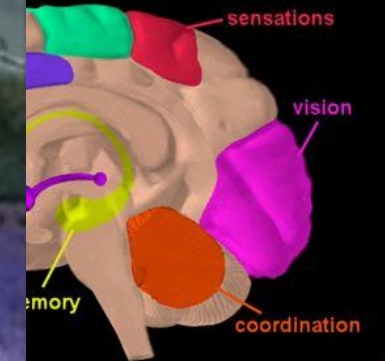
Cannabis sativa

- THC →
- CBD →



on and

n memory,



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)



Part III: Cannabis and Cognition

■ Sex/gender Differences

- Neurodevelopment occurs earlier in females compared to males
- Females show greater CBI desensitization to THC
- Males have greater CBI 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

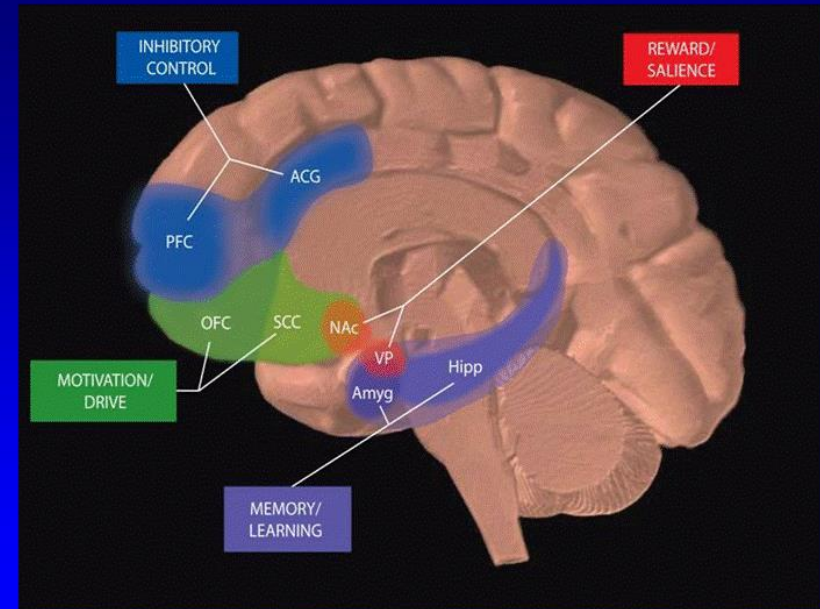


Cognitive Bias

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

Circuits Involved In Drug Abuse and Addiction



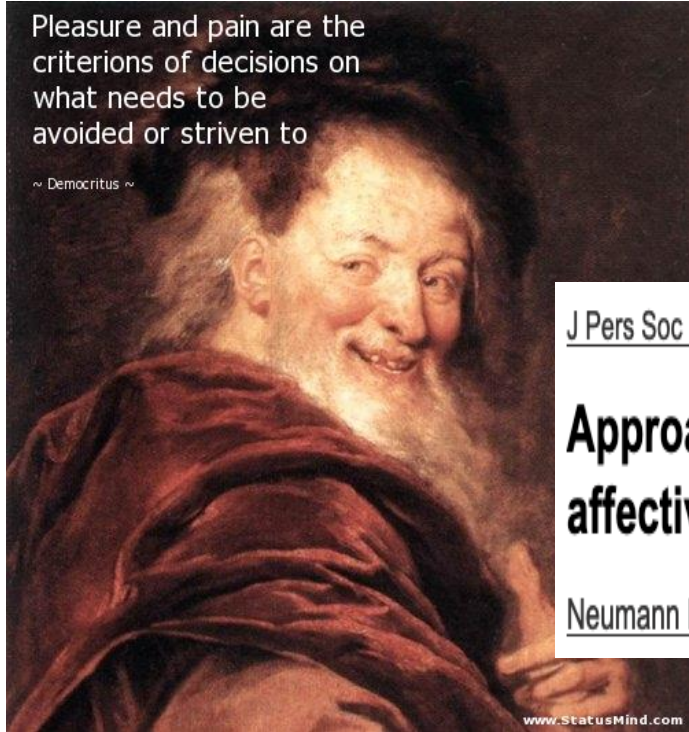
All of these brain regions must be considered in developing strategies to effectively treat addiction

NIDA

Cannabis and Cognitive Bias

Pleasure and pain are the
criteria of decisions on
what needs to be
avoided or striven to

~ Democritus ~



reaction to
which



behavior following exposure to
individual's awareness.

J Pers Soc Psychol. 2000 Jul;79(1):39-48.

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

Neumann R¹, Strack F.

www.StatusMind.com

■ increased use, greater problem severity at 3 year follow-up

Democritus (460 – 370 BCE)

- Women may be more responsive to cognitive bias retraining (i.e. subliminal priming study) (Wetherill et al. 2015)

William James

Principles of Psychology (1890)



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:**

- Aim 1: Does ABM reduce cannabis approach bias?

- Aim 2: Does ABM reduce cannabis cue reactivity?

- Aim 3: Does gender moderate 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



to irrelevant stimulus feature (i.e. border color)

h (pull)/avoida
imental) or S
Pull MJ_RT).



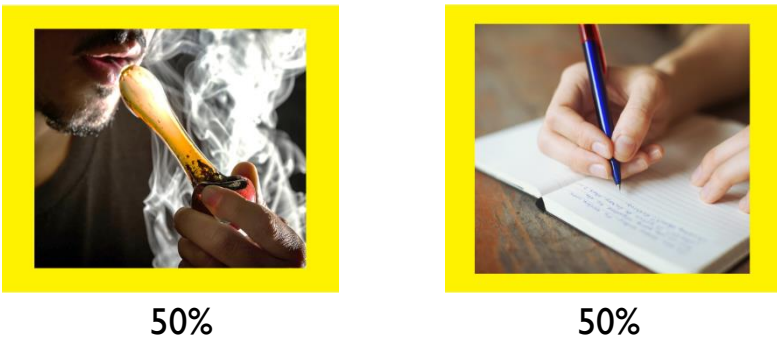
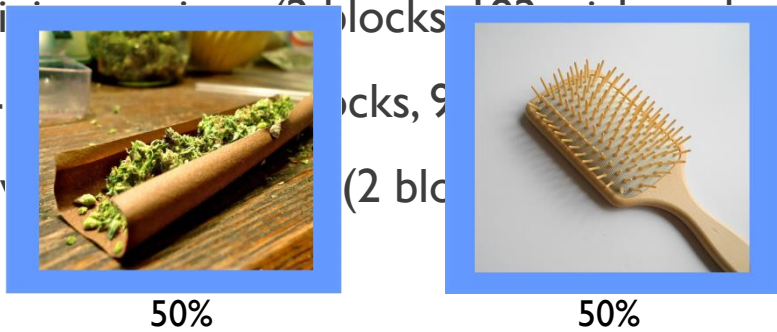
M-AAT



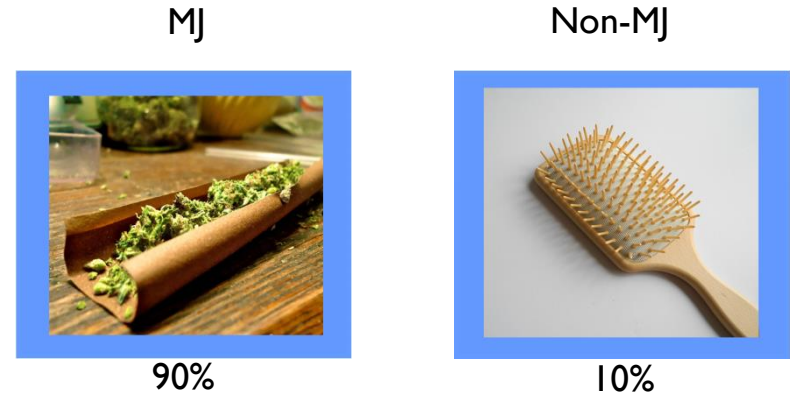
M-AAT

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

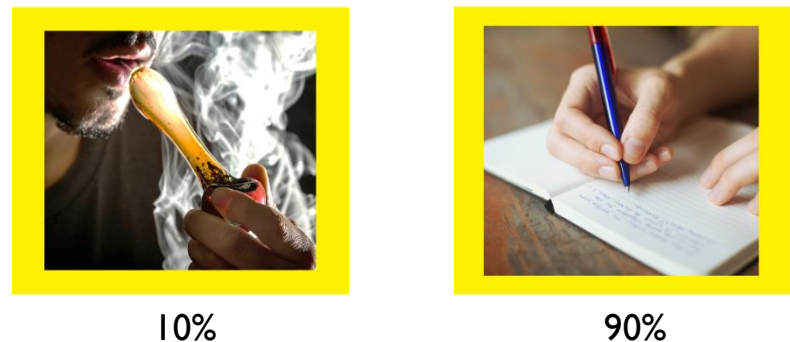
Sham training



Active training



Push



Pull

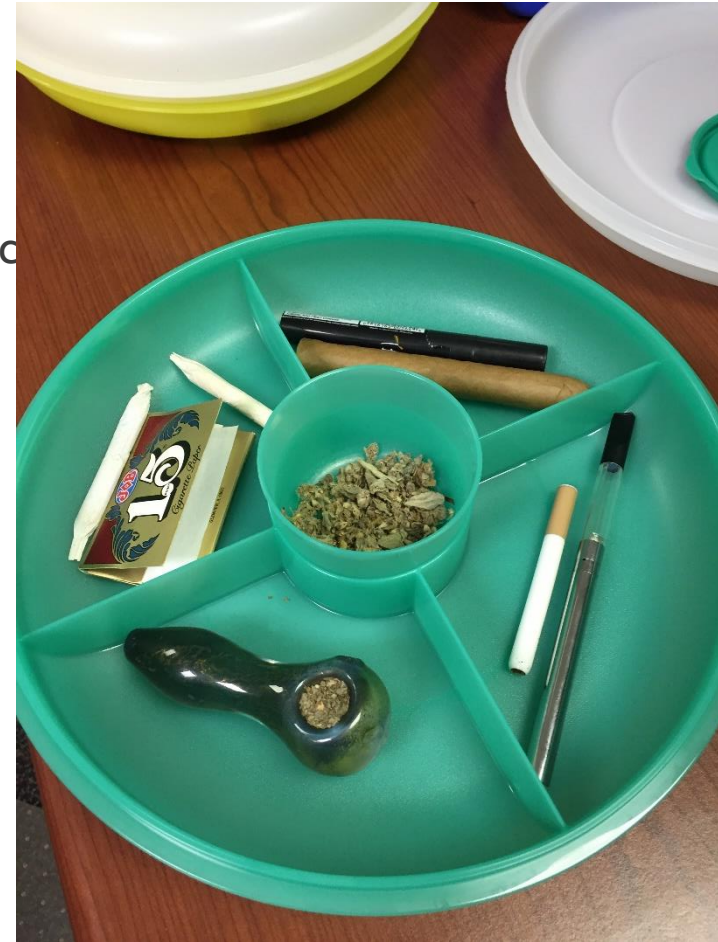
Cue reactivity

- Live cue e
- Outcome

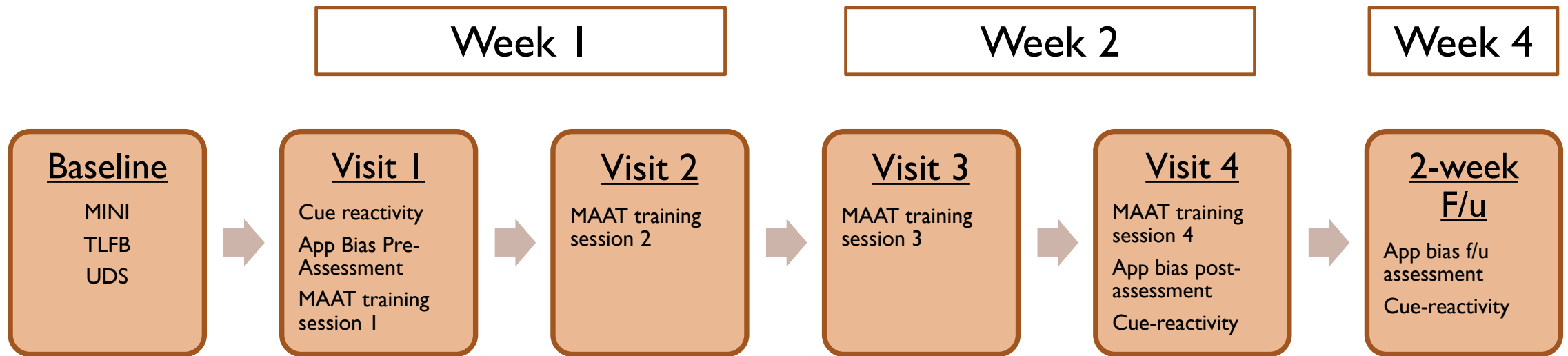


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Study Timeline



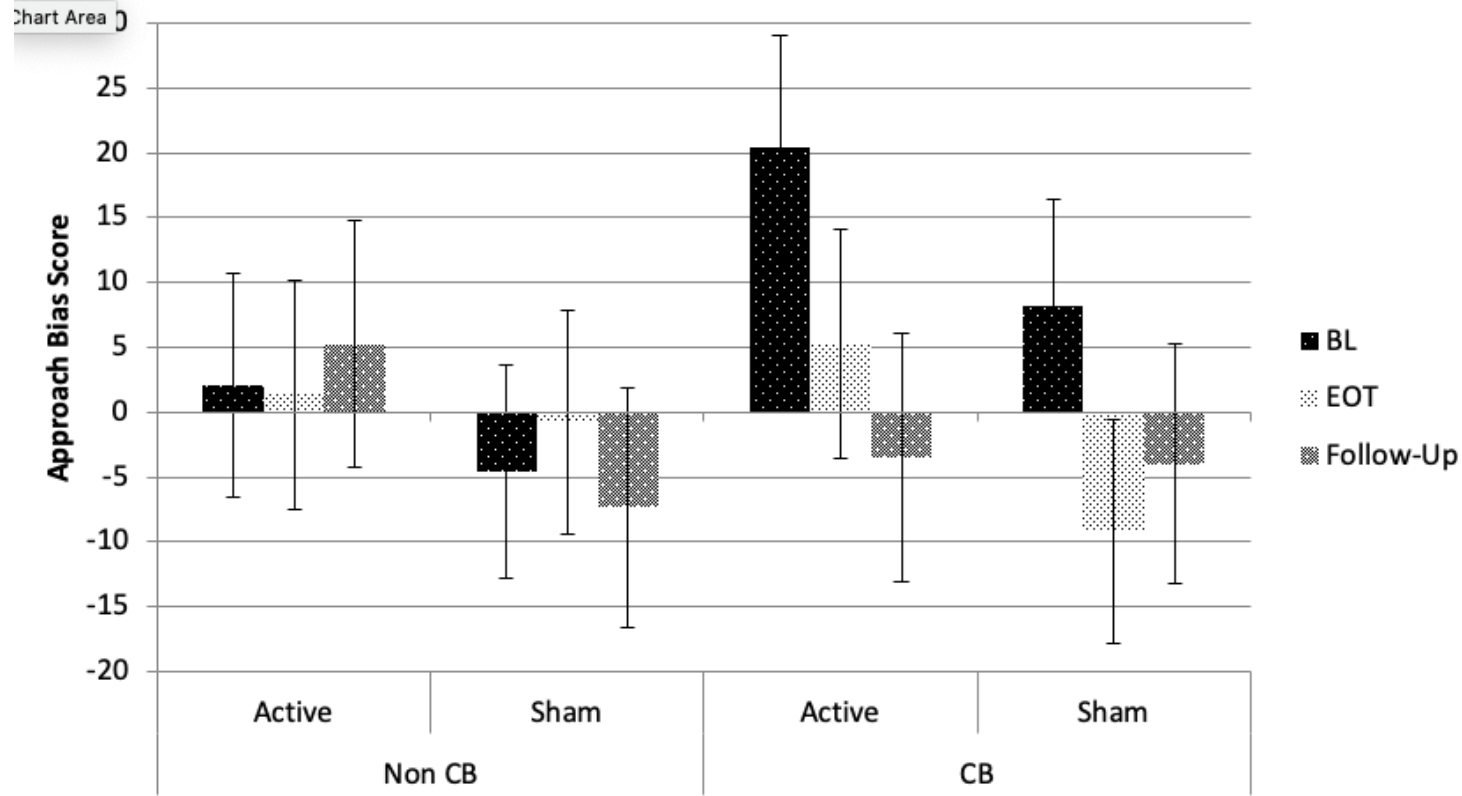
Results

- 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



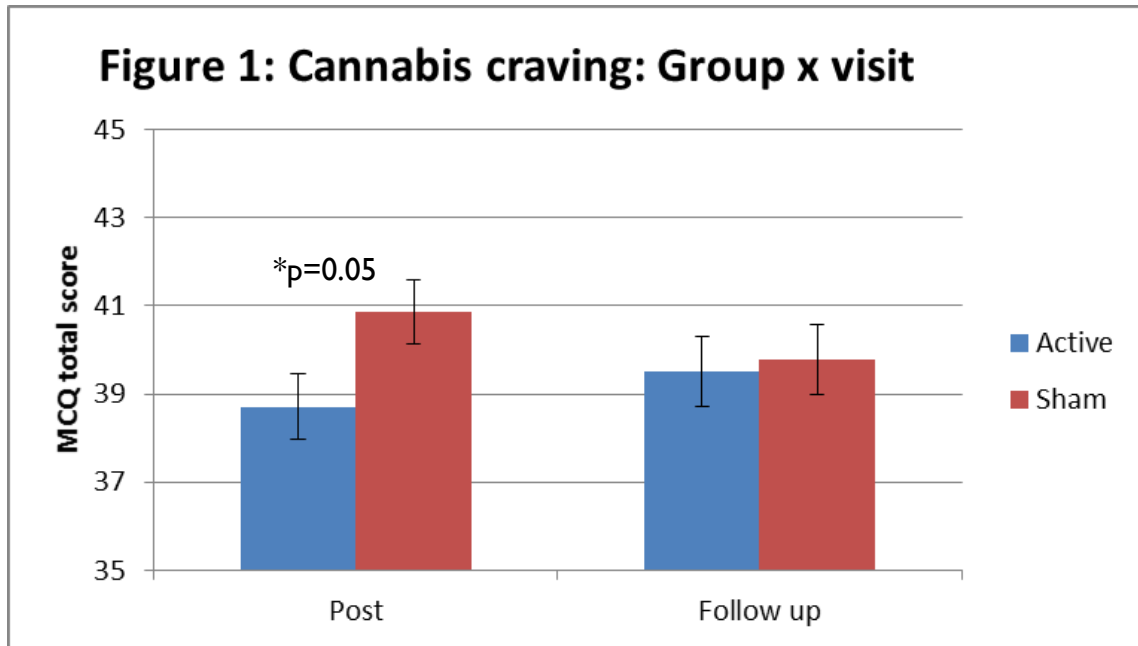
Results – Specific Aim 1: MJ Approach Bias

Figure 1: Approach bias scores by condition, valence, and visit



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.

Figure 1a. Visit 4 cannabis craving by valence.

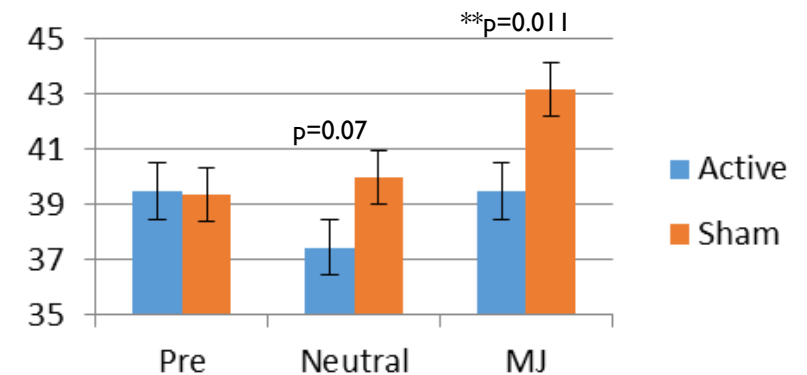
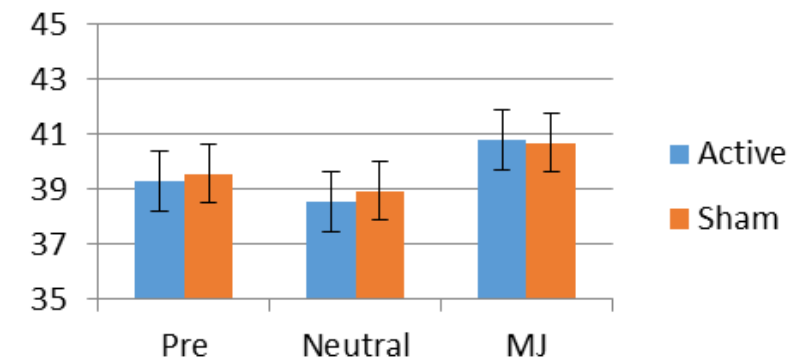
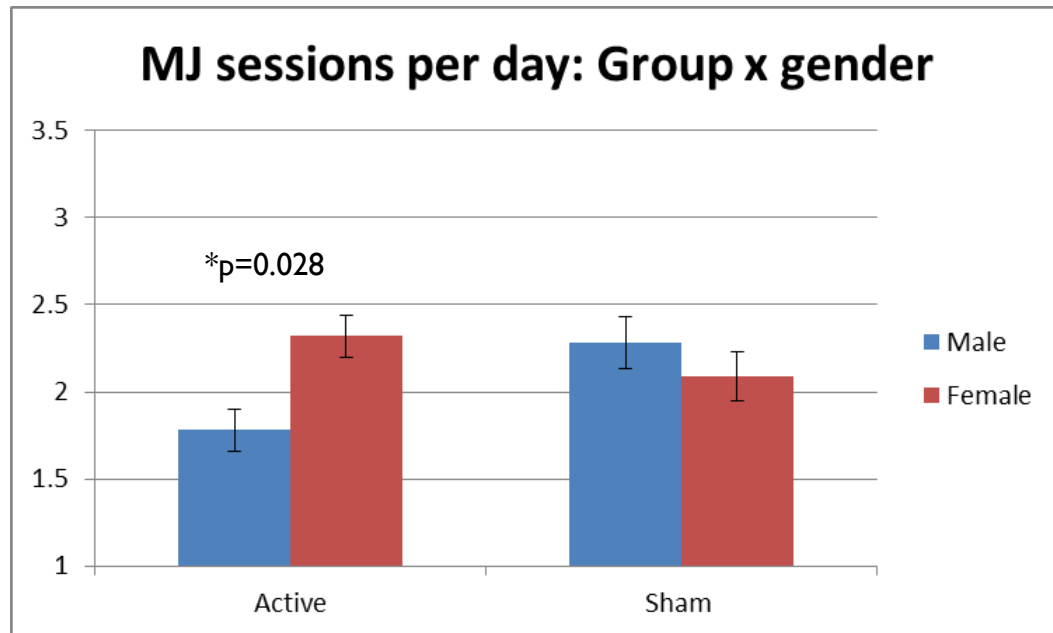


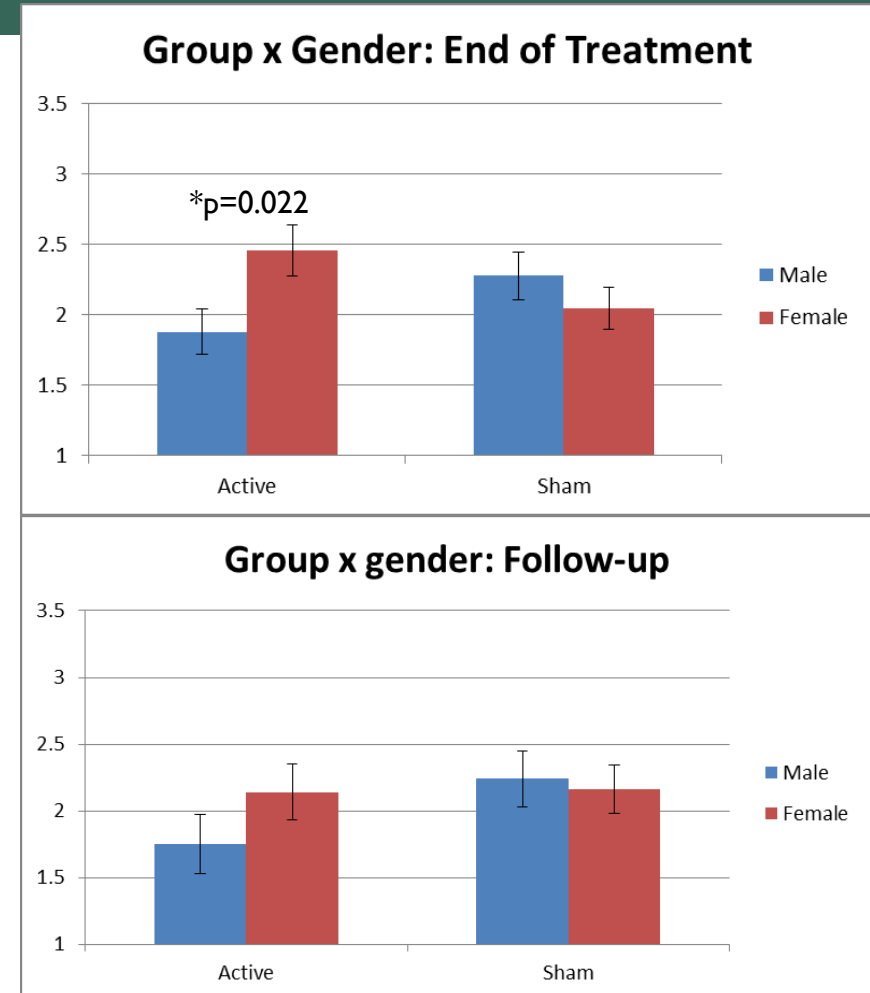
Figure 1b. Follow-up cannabis craving by valence.



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

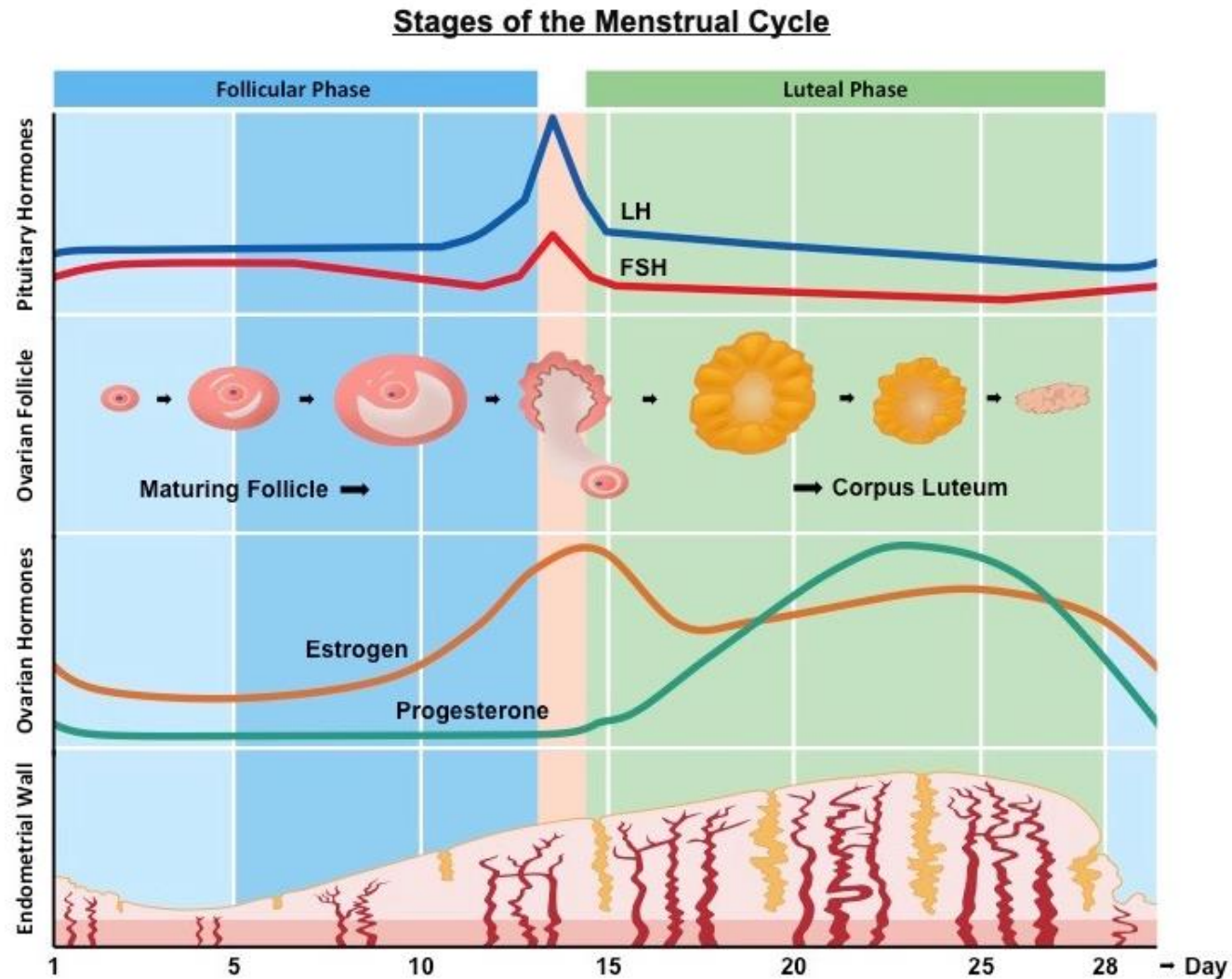
1. No treatment effect of ABM on cannabis approach bias.
2. Blunted cue-reactivity in treatment group at end-of-study.
3. Men reported fewer sessions/day at end of study compared to women.

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



Exp Clin Psychopharmacol. 1999 Aug;7(3):274-83.

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

Sofu *Nicotine Tob Res.* 2015 Apr;17(4):398-406. doi: 10.1093/ntr/ntu262.

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

Saladin ME¹ **Addiction** 
RESEARCH REPORT doi:10.1111/j.1360-0443.2008.02146.x

Menstrual phase effects on smoking relapse

Progesterone 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



Exogenous progesterone for cannabis withdrawal in women: Feasibility trial of a novel multimodal methodology.

Sherman BJ¹, Caruso MA², McRae-Clark AL³.

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's; Urine cannabinoid levels

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

Study Design

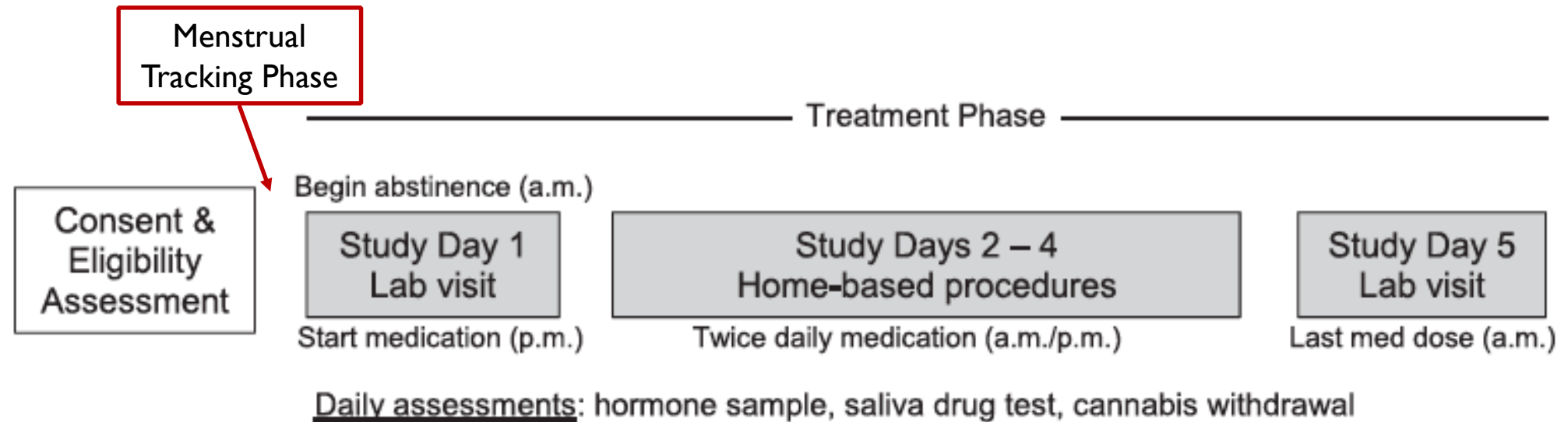


Fig. 1. Study design and timeline.

Procedures:

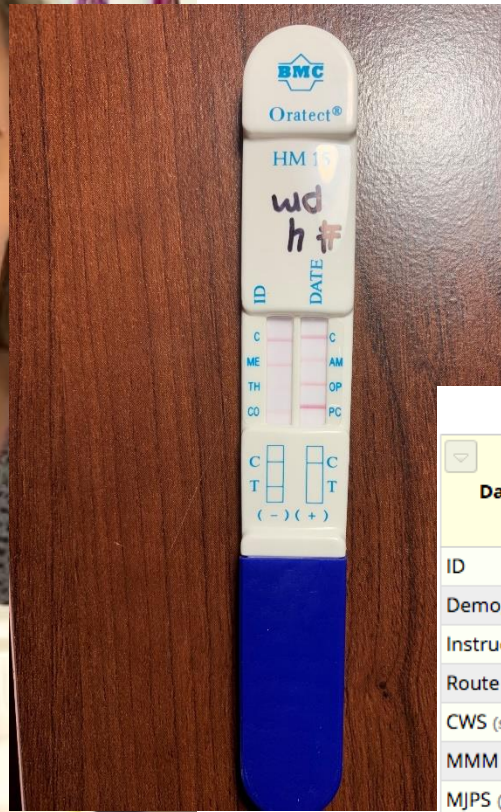
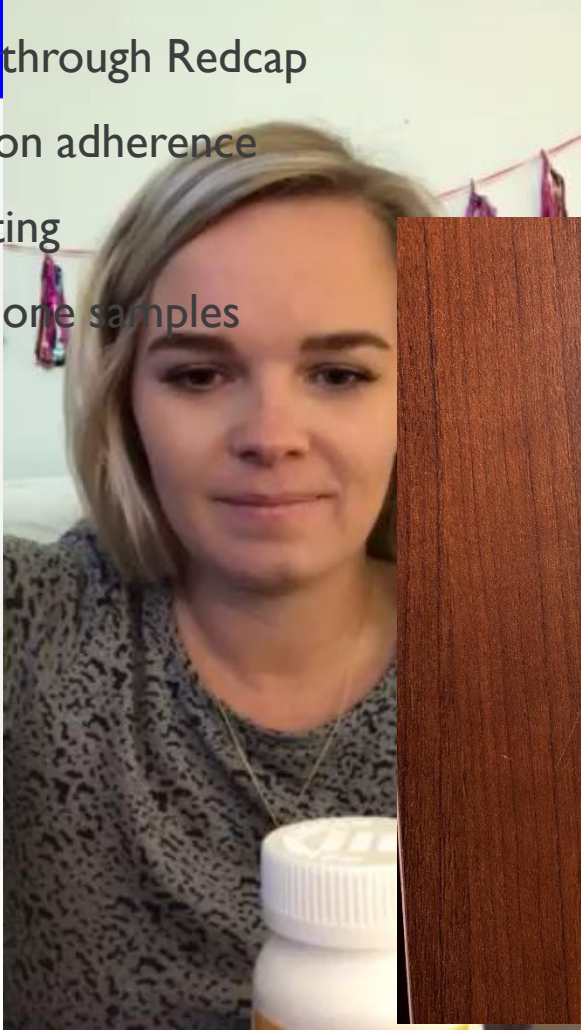
You have a session waiting.
Please respond.

■ EMA surveys through Redcap

SCORE Cannabis
■ Tele-medication adherence
Day3 amVideo1

Waiting
■ Tele-drug testing

■ Salivary hormone samples



Participant ID 6003

Data Collection Instrument	Screening	BL/Study Visit 1	Study Visit 2	Study Visit 3	Study Visit 4	Follow-Up	6-month F/u
ID	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Demographics (survey)	<input checked="" type="checkbox"/>						
Instructions (survey)	<input checked="" type="checkbox"/>						
Route of admin (survey)	<input checked="" type="checkbox"/>						
CWS (survey)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
MMM (survey)	<input checked="" type="checkbox"/>						
MJPS (survey)	<input checked="" type="checkbox"/>				<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
RFQ (survey)	<input checked="" type="checkbox"/>						
MJ Ladder (survey)	<input checked="" type="checkbox"/>						
SOCRATES (survey)	<input checked="" type="checkbox"/>				<input checked="" type="checkbox"/>		

Results

Table 1. Descriptive characteristics for full sample and by condition.

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

Note: PROG = progesterone condition, PBO = placebo condition.



Results

Aim I: Feasibility

I. 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

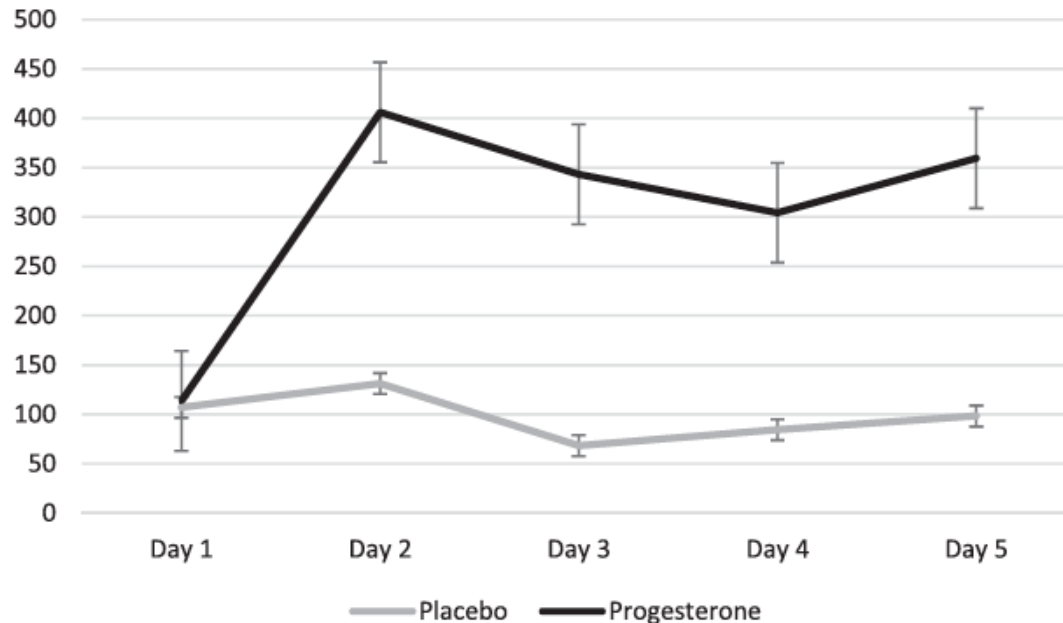


Fig. 2. Progesterone levels (pg/ml) by treatment condition and time.

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

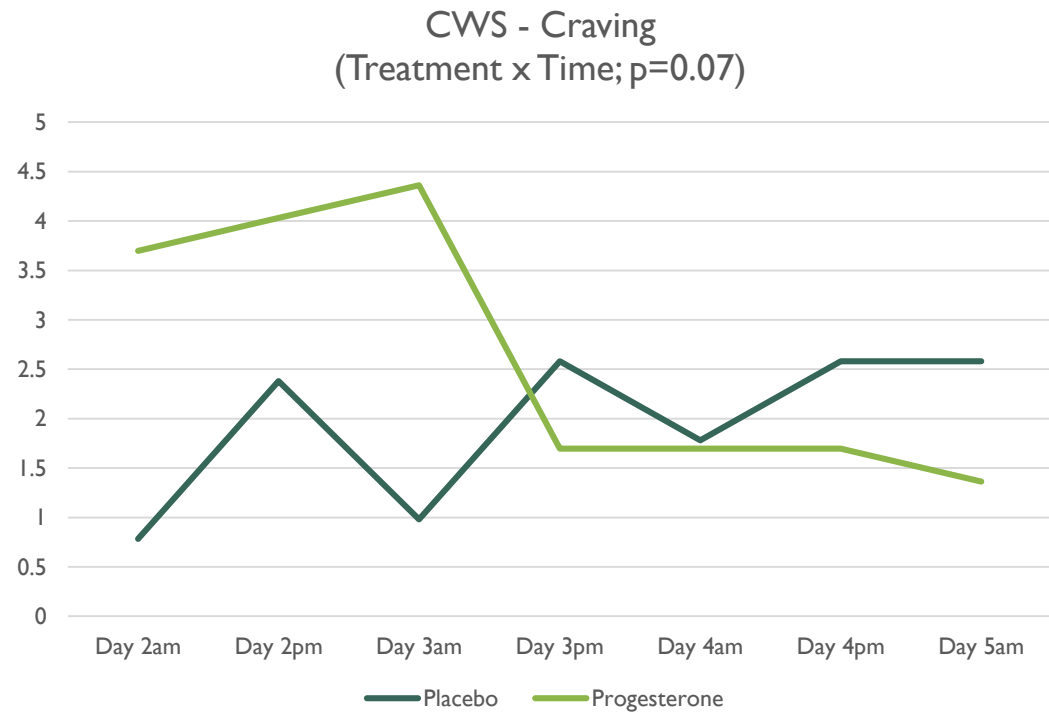
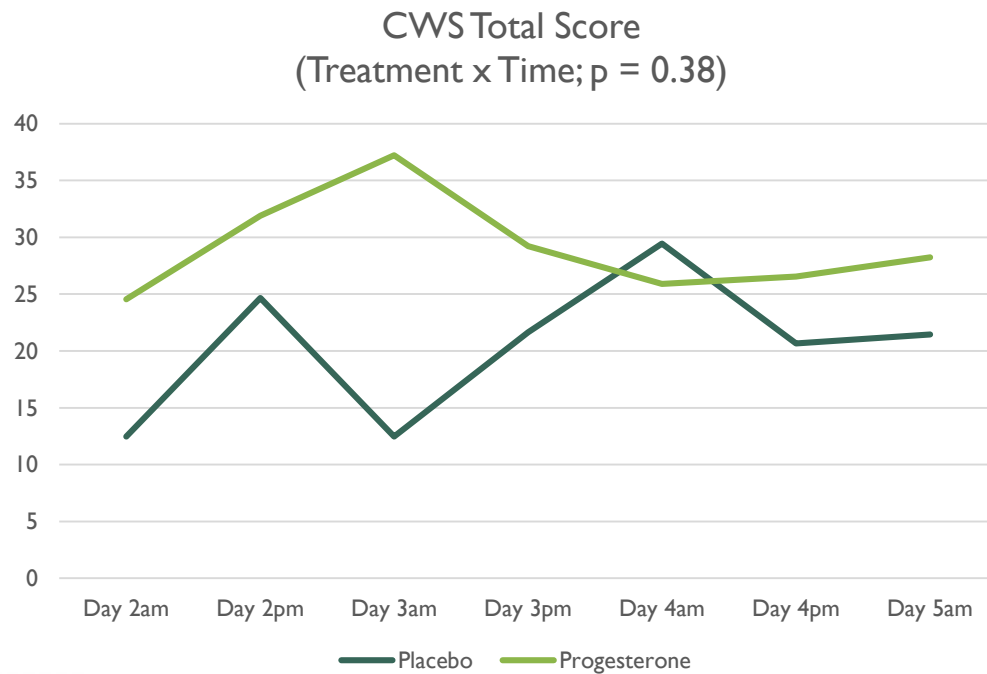
1. 100% (40/40) saliva samples were THC negative
2. Urine cannabinoids decreased 56% from Day 1 to Day 5, (582.21 ng/ml → 258.07 ng/ml; $p = 0.06$)
3. Self-reported abstinence 100%
4. Groups did not differ ($p = 0.36$)



Results

Aim 2: Cannabis Abstinence and Withdrawal

Cannabis withdrawal



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)

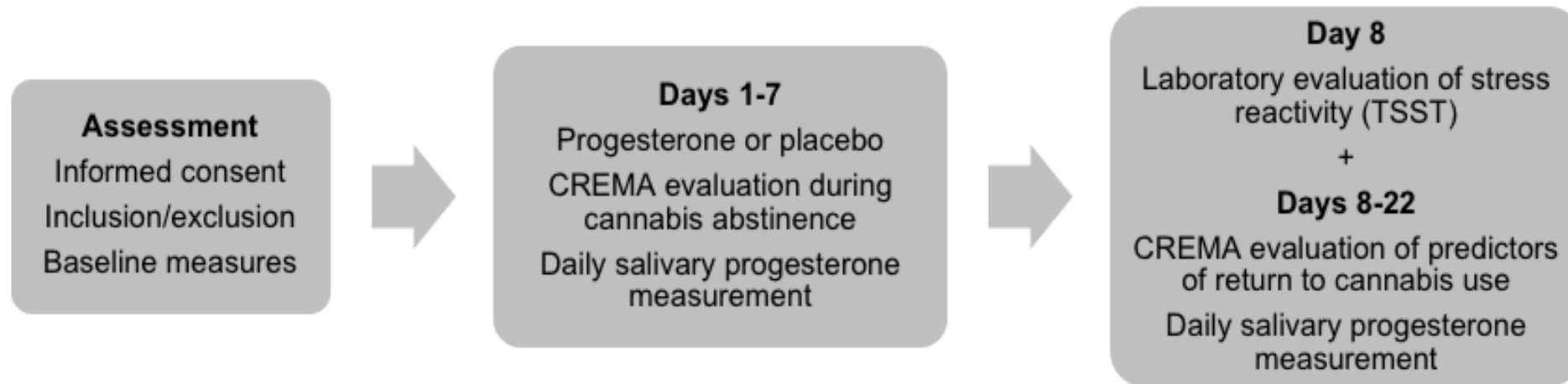
2. Ovarian Hormones

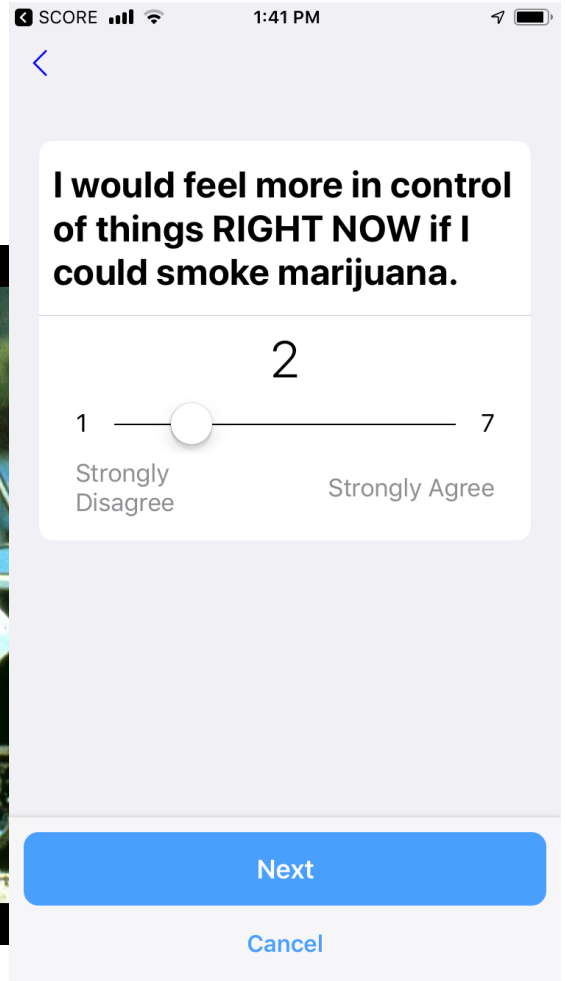
- a) U54 SCORE (McRae-Clark) Progesterone for cannabis withdrawal and stress reactivity
 - Does progesterone reduce stress-reactivity (i.e. stress, drug craving) in females with CUD, compared to males?
 - Does baseline cognitive functioning (cognitive bias) moderate treatment effect?
 - Does progesterone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



Specialized Center of Research Excellence on Sex Differences (SCORE)

I. Component I: “Impact of progesterone on stress reactivity and cannabis use”





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??