

Cannabis Misuse and Cannabis Use Disorder: Prevention and Intervention Approaches

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Disclosures

- Training and Research: funded for ~ 30 years by **NIH-NIDA**
- National Advisory Council / Scientific Advisory Board:
Center for Medical Cannabis Research (UCSD), State of CA
- DSM-5 Substance Use Working Group / Revision Panel

I don't currently use cannabis, THC, cannabinoids or CBD
Strong bias against "Medical Marijuana Laws"!

AGENDA

- 1) Rationale for focus on Cannabis
 - addictive potential & consequences of THC-laden cannabis
- 2) Review clinical/intervention research
- 3) Current and future directions
- 4) Public Health Issues / Need for Cannabis Regulatory Science

Define Cannabis (Marijuana)

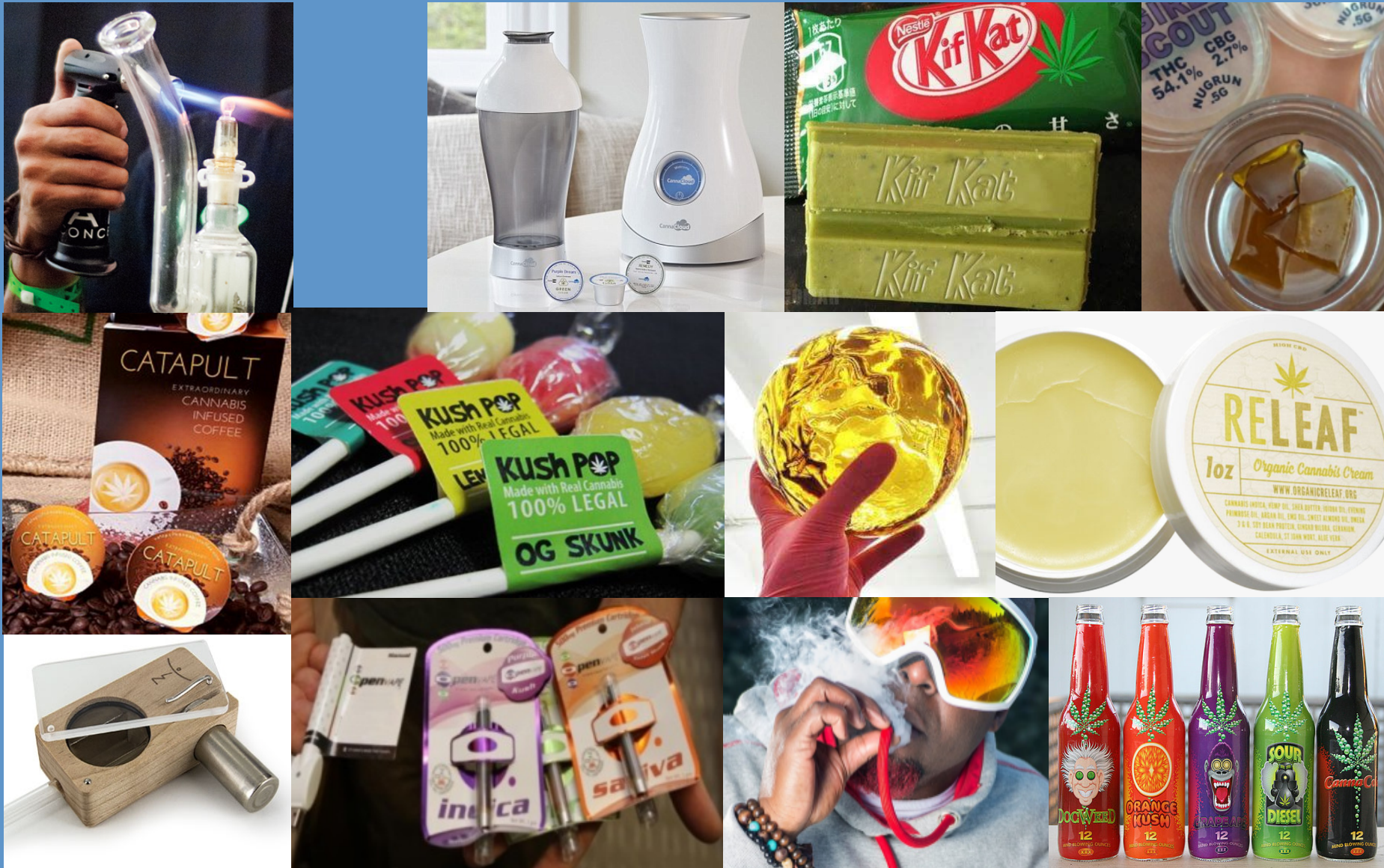
- Cannabis Plant: *sativa, indica*
- Over 100 compounds
- Differentiate Compounds: THC from CBD
 - ** cannabinoids



Major / Minor Cannabinoids?

- **** THCA (Δ^9 -tetrahydrocannabinolic acid)**
 - intoxication, cognitive, motor, psychosis
- **CBD A (Cannabidiolic acid)**
- CBGA (Cannabigerolic acid)
- CBCA (Cannabichromenenic acid)
- CBGVA (Cannabigerovarinic acid)
- THCVA (Tetrahydrocannabivarinic acid)
- CBDVA (Cannabidivarinic acid)
- CBCVA (Cannabichromevarinic acid)
- **Terpenes:** essential oils, smells, flavor
- *Entourage Effect*

Misuse and Addiction: Cannabis Products (THC)



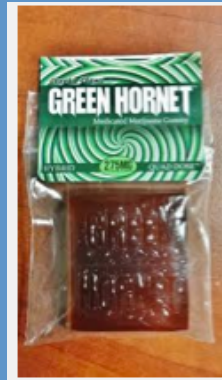
Cannabis Products: Smoking / Vaping



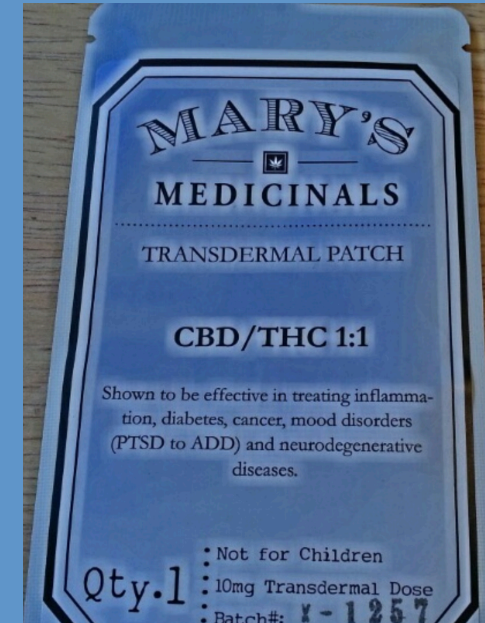
High Potency Products – Buds and Concentrates



Edibles



Lotions / Cremes / Salves / Patches



Misuse and Addiction: Not CBD-only Products



Addiction / Adverse Consequences

Data: Starting Point

Cannabis (THC-laden) is addictive in every accepted scientific and clinical meaning of that concept

Science / evidence for this is strong / unambiguous

Evidence: Addictive Potential & Clinical Consequences

Biological, Behavioral, Epidemiological

- Endogenous cannabinoid system in the CNS
- Effects of administration and cessation on brain reward centers are similar to other drugs with addictive potential (CB1R)
- THC functions as a reinforcer in the human lab
- Clinically meaningful withdrawal syndrome
- Clinical Epidemiology: People meet CUD criteria
- Treatment seeking for CUD is prevalent
- Treatment response is modest; difficult to quit; high rate of relapse

Potential Negative Consequences Cannabis (THC-laden)

Cognitive Functioning (learning / memory / attention)

- Acute (short term); Chronic (long term)
- Neurodevelopment

Accidents – e.g., impairs driving

Mental Health

- Acute; Chronic

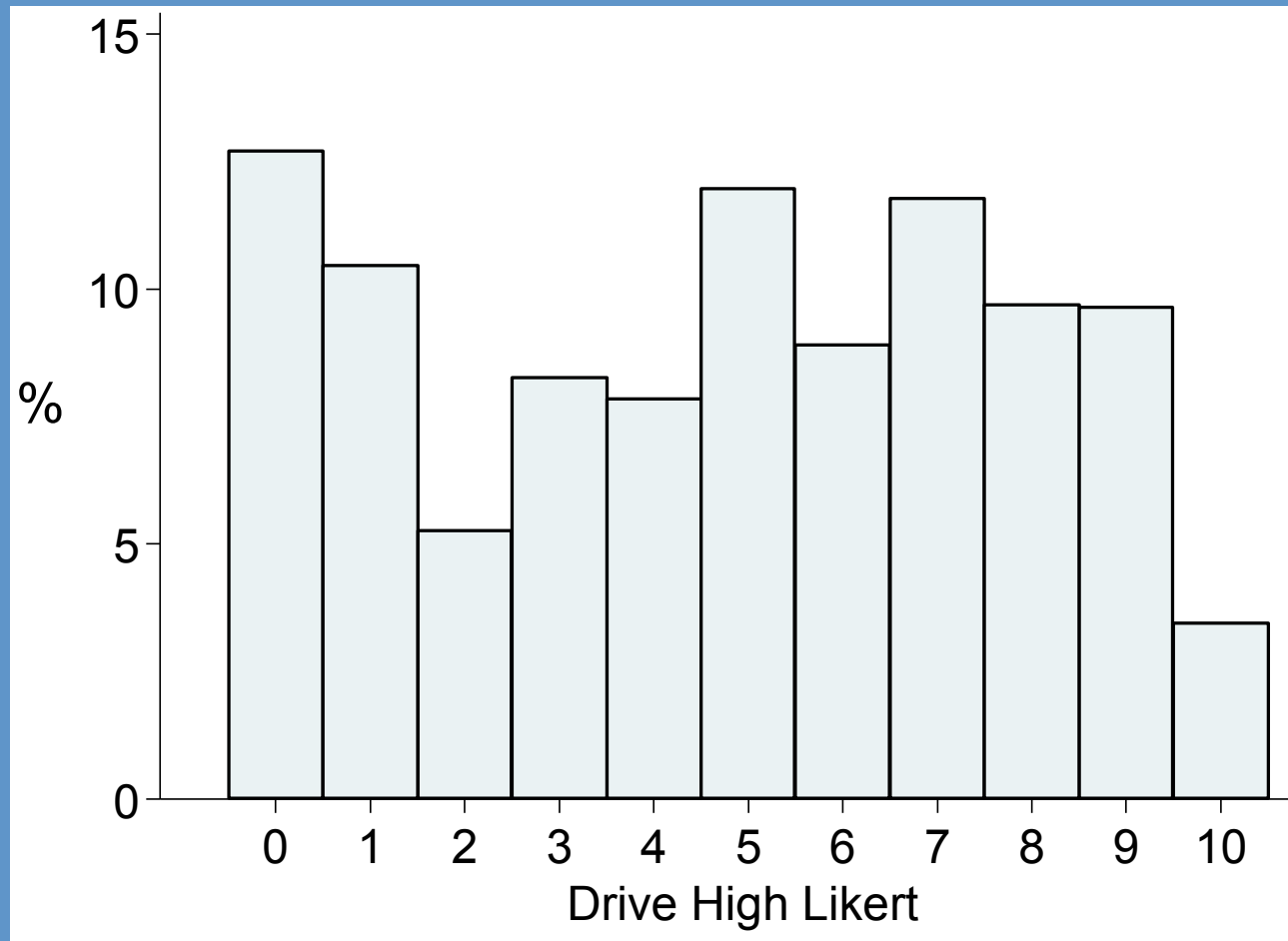
Respiratory (smoke or vape)

Cardiovascular

Perinatal Outcomes

Digital Epidemiology Survey (N=4177 current users)

“How high could you get and still drive safely?”



Mean: 4.7 (3.1)



Borodovsky et al., in press

***“Think about how high you typically get when you use cannabis.*
In the past 30 days how many days have you driven a car
*within 2 hours after getting that high?”***

	N	%
0 days	727	23.6
1-2 days	533	17.3
3-5 days	350	11.4
6-9 days	284	9.2
10-19 days	401	13
20-25 days	243	7.9
26-29 days	121	3.9
All 30 days	421	13.7

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 cannabis (conditional probability will develop problems (10-30%))

Problems will range from mild to severe

Vulnerable Populations

Highest Rates of CUD / 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

Interventions for CUD and Misuse

What Treatments Approaches are Effective and How Effective are They

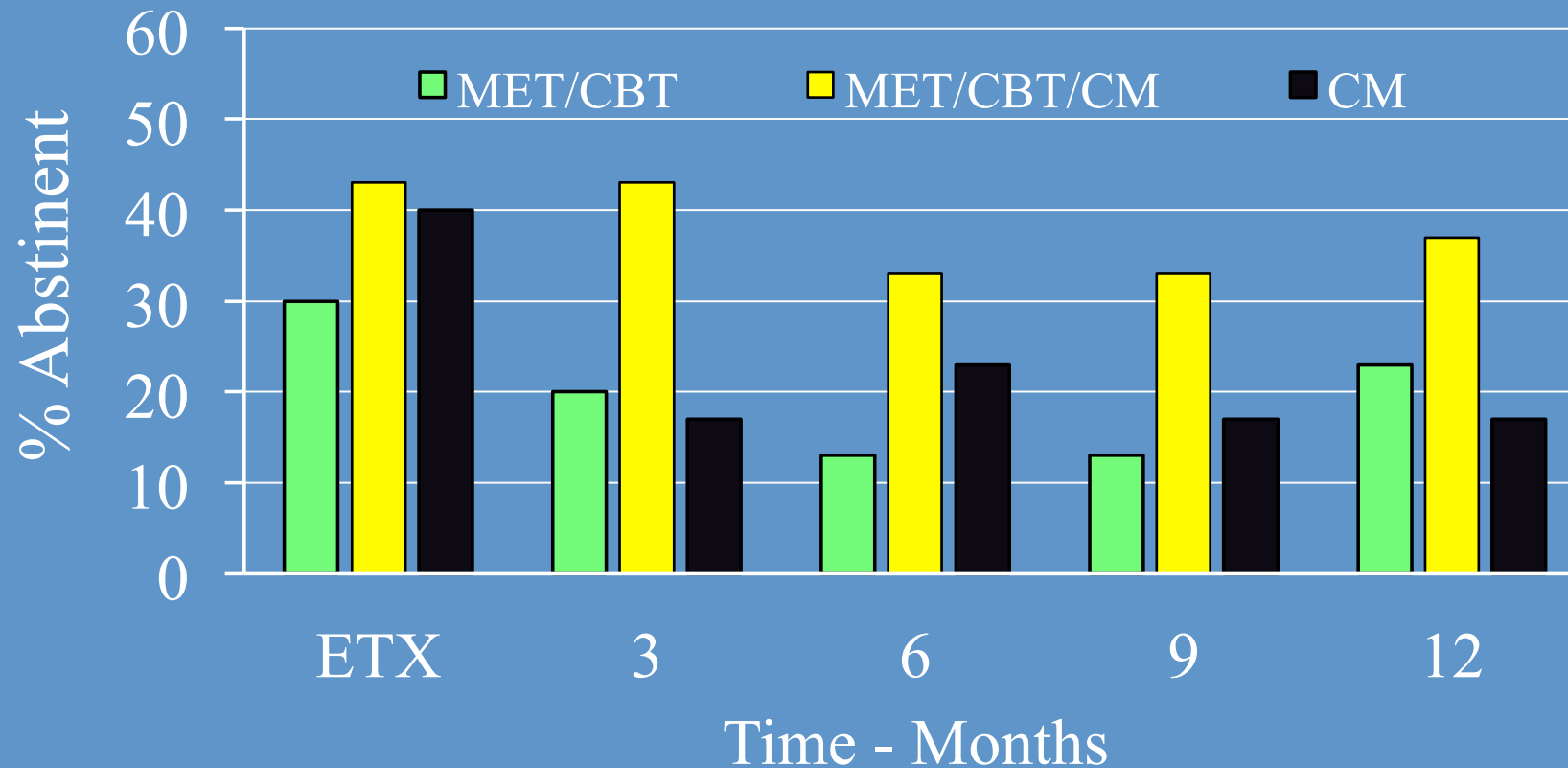
- Motivational Enhancement Therapy (MI / MET)
- Coping Skills Training (BT / CBT)
- Contingency Management:
- Family-based Treatments for Adolescents

Adult Treatment Studies

CM Improves Abstinence Outcomes

MET/CBT Maintains Abstinence

Replication and Extension (Budney et al. 2006)



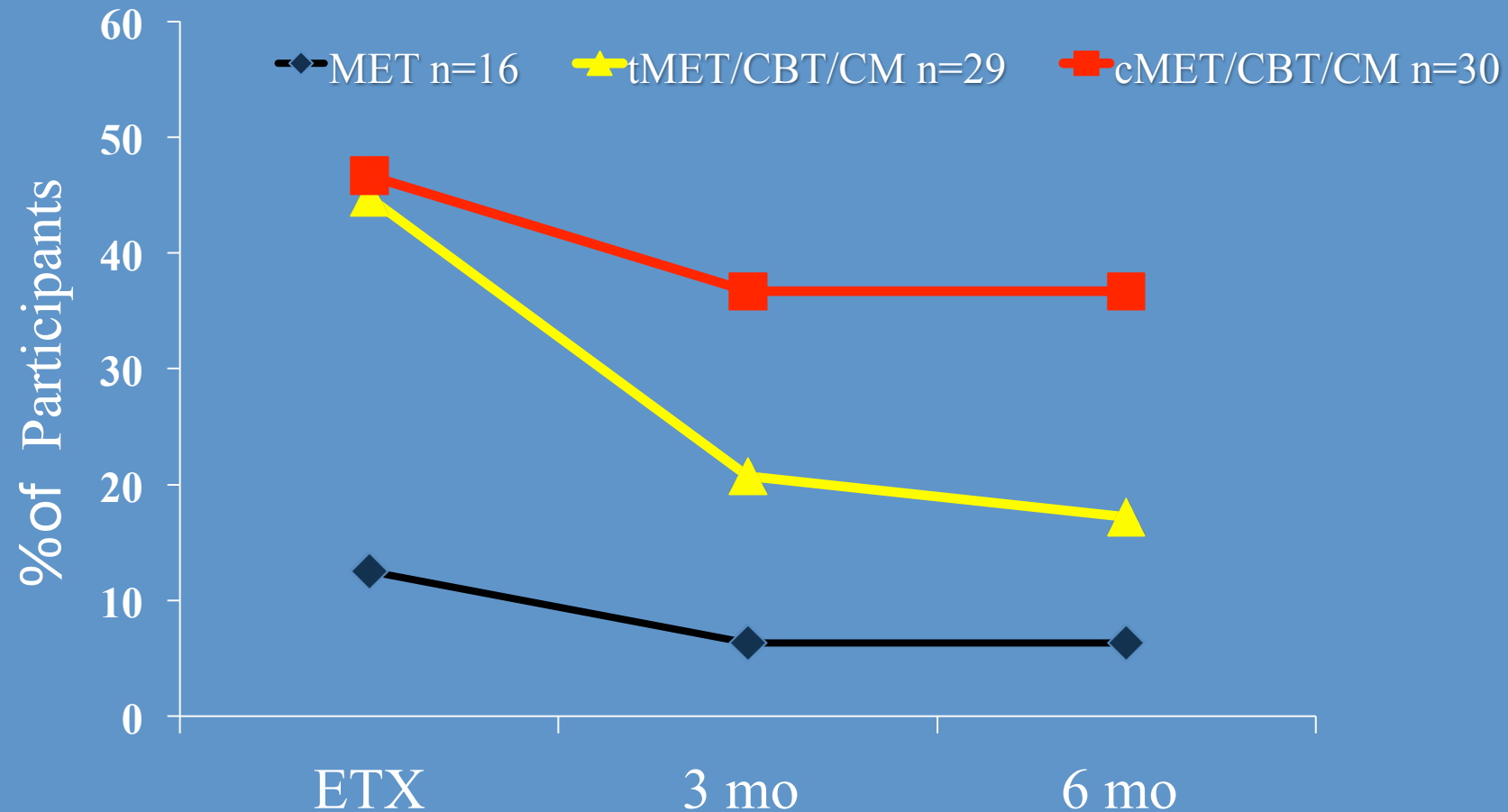
MET/CBT/CM: gold standard - replicated in Carroll et al, 2006 and Kadden et al., 2007

MET/CBT/CM: Computer-assisted vs. Therapist-delivered

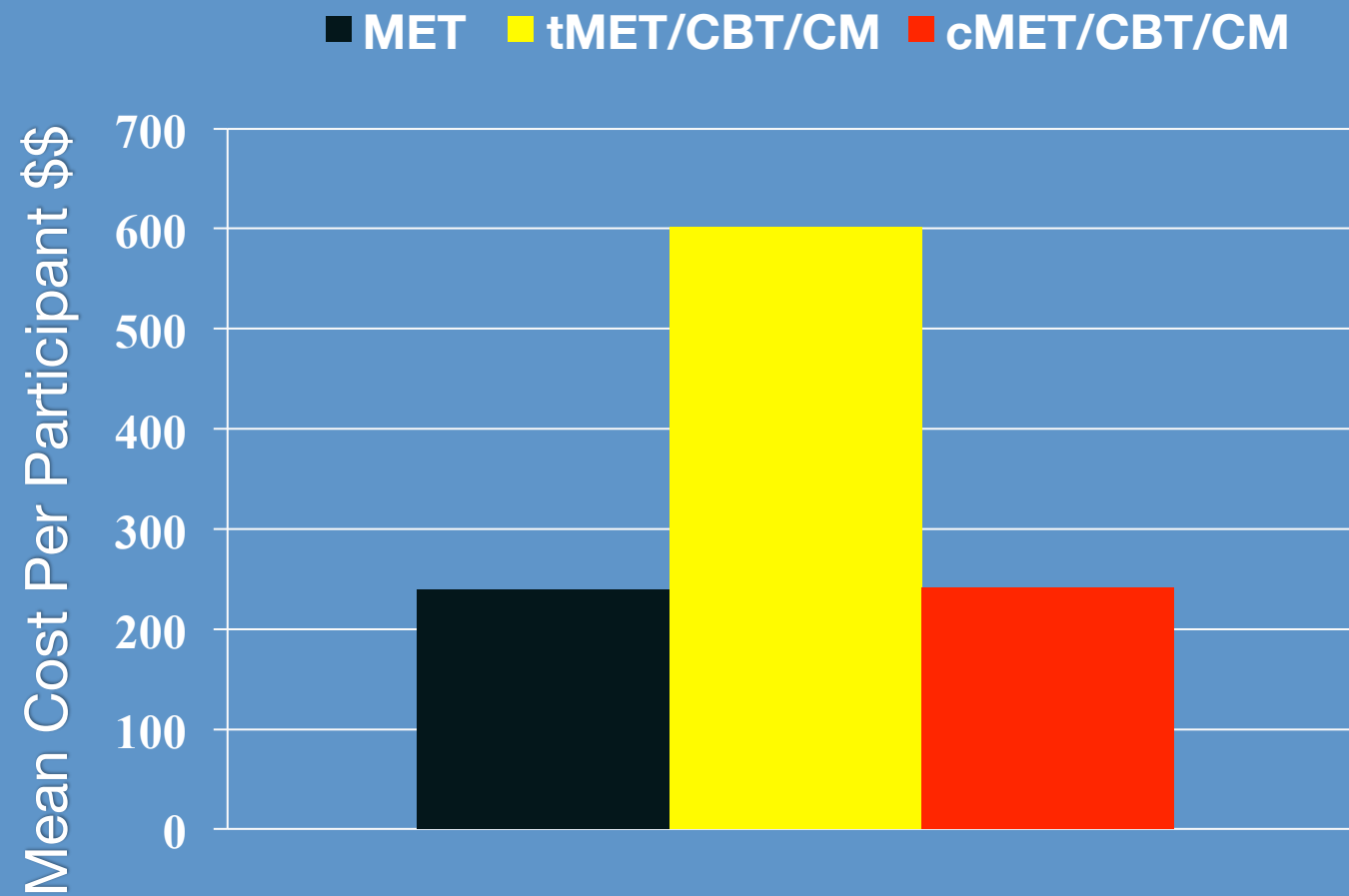
- Enhance Dissemination / Fidelity

↑ Access and ↓ Cost

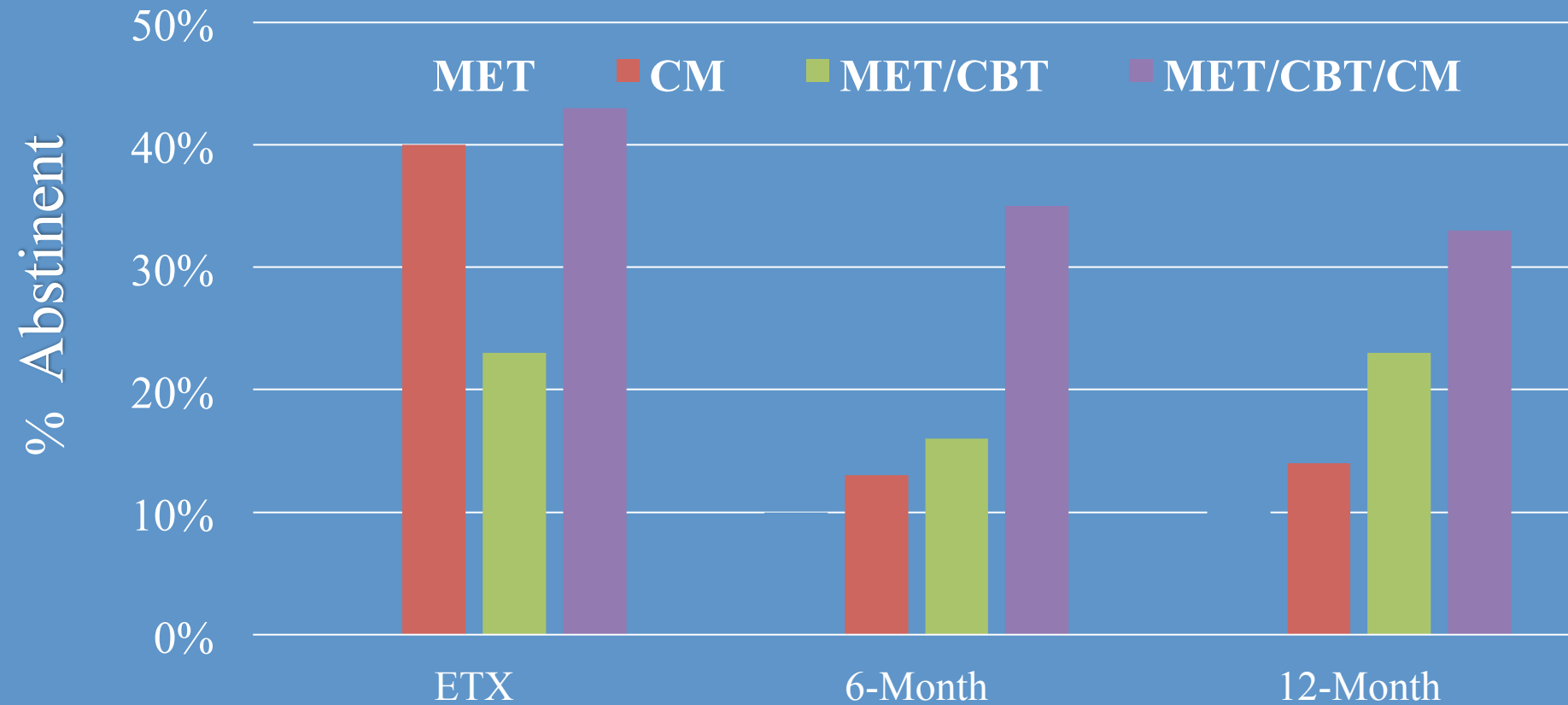
(Budney et al. 2015, 2011)



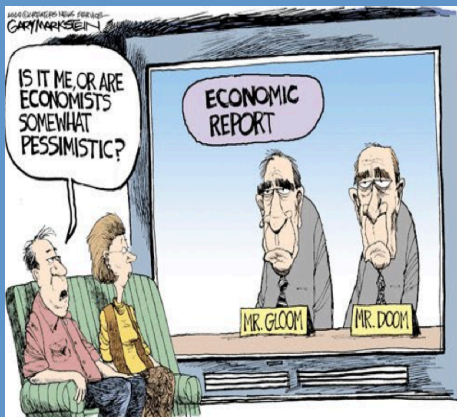
Cost



Abstinence Outcomes Across Multiple Studies

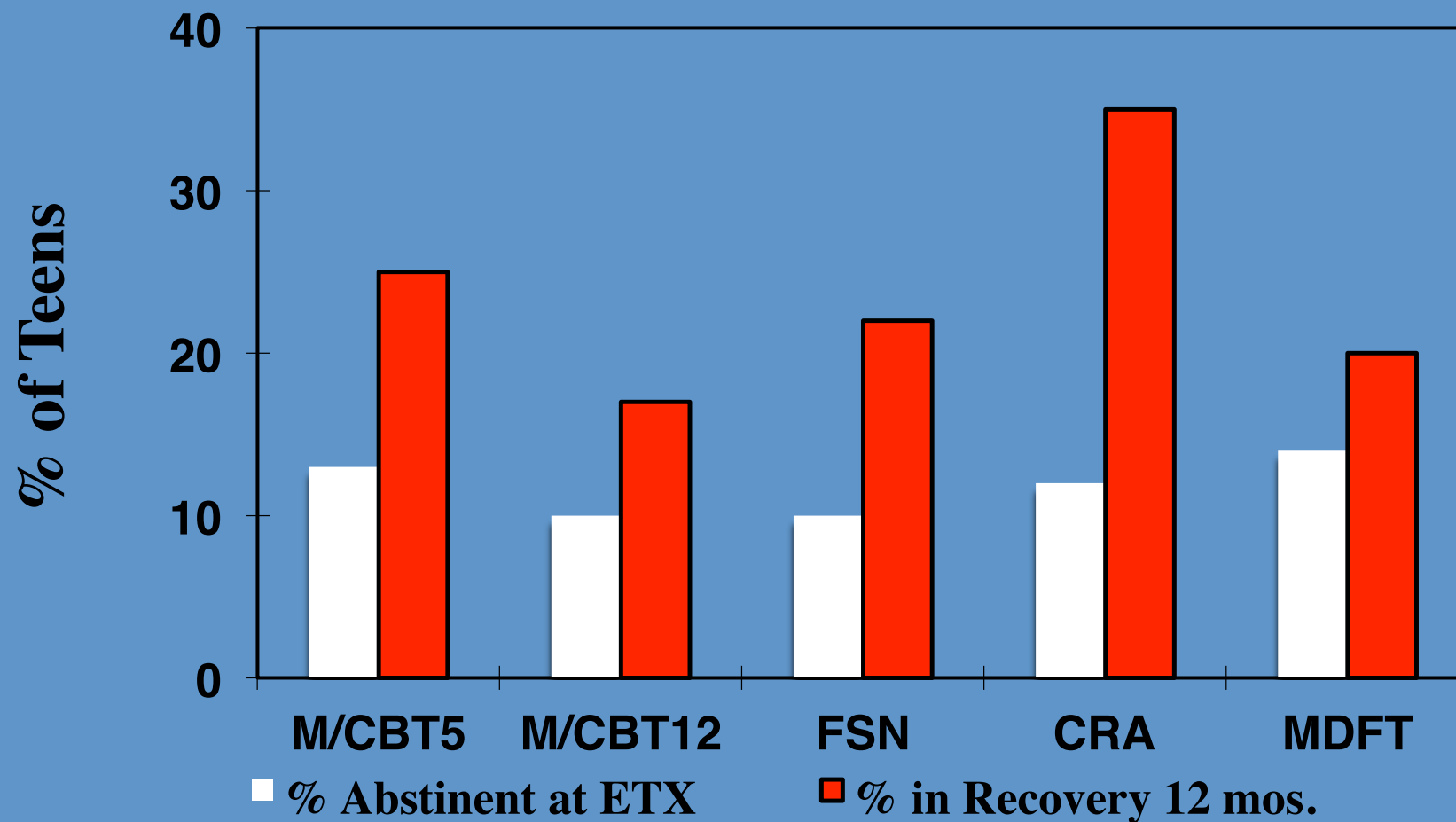


Adolescent Treatment



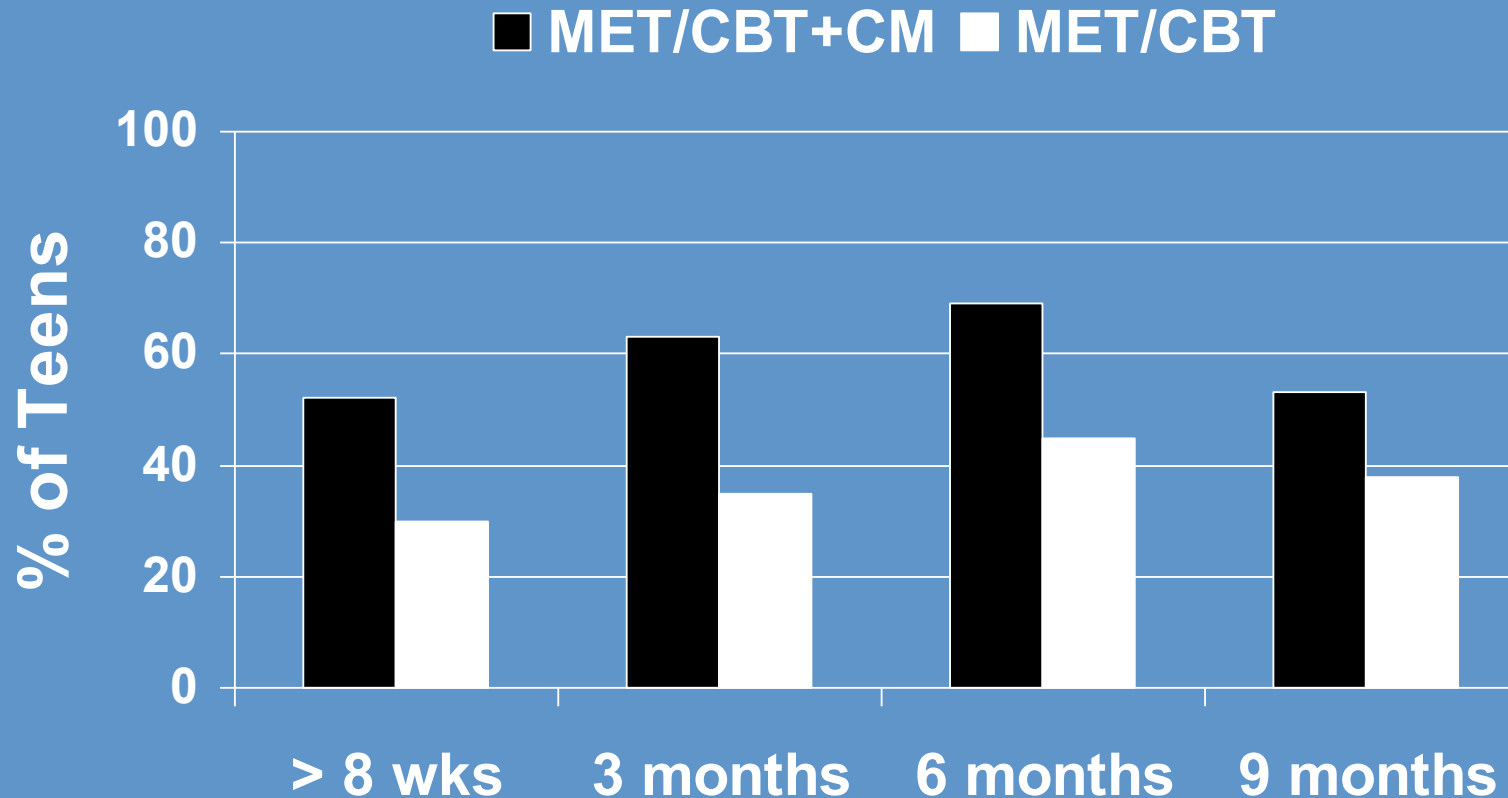
Youth: + Family-based Interventions

Cannabis Youth Treatment Study



(Dennis et al., 2004)

* CM Improves Abstinence Outcomes for Adolescent CUD



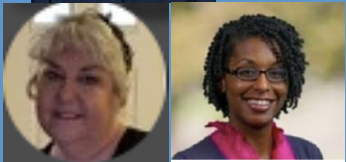
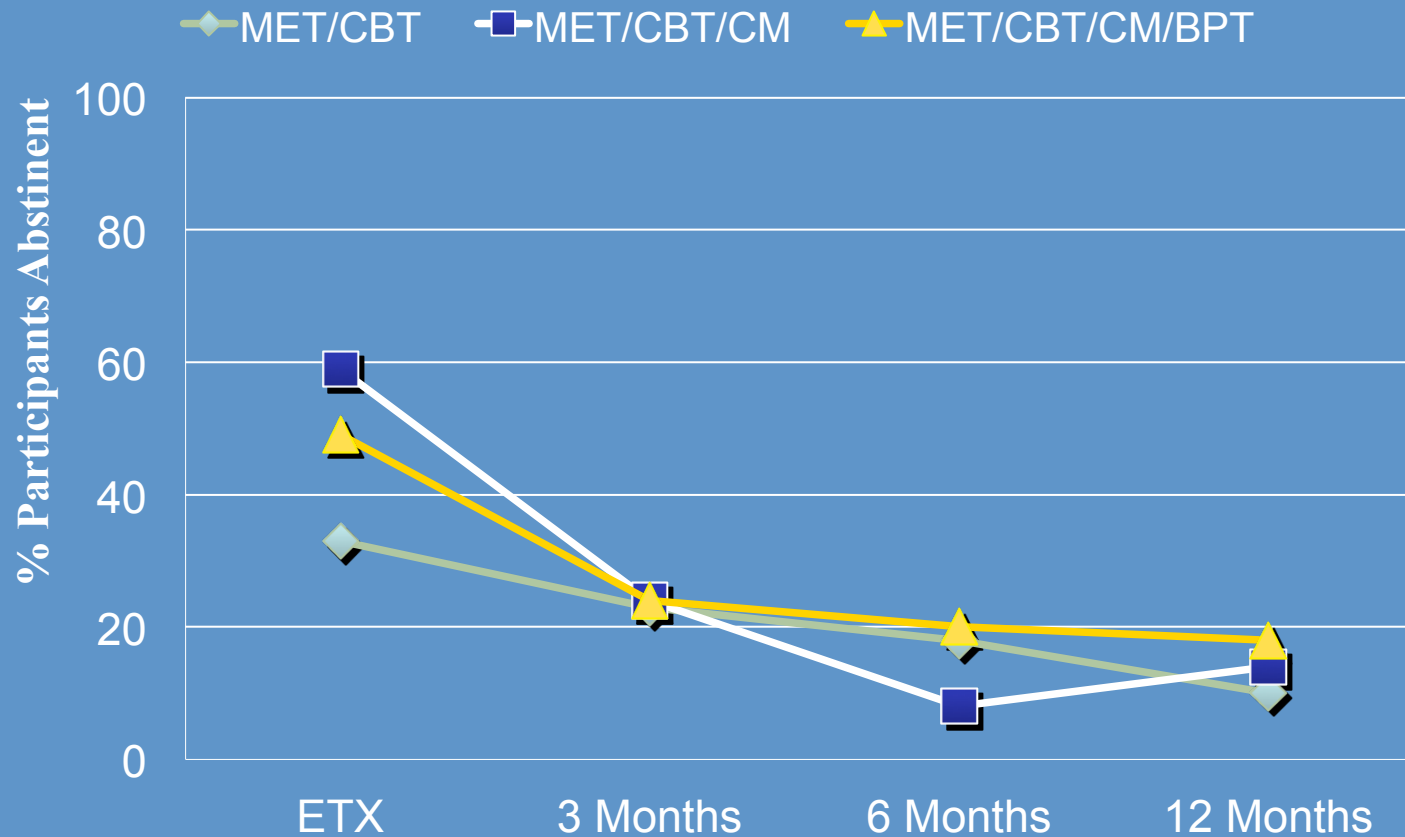
* CM: clinic and family-based

Stanger, Budney, Kamon, et al. (2009)

CM for Adolescents: Replication and Extension

CM enhanced outcomes, but did not maintain

(Arkansas: Stanger et al., 2015)



How Do We Improve?

Behavioral Science and Neuroscience Provide Targets

- Enhance Delivery Systems / Improve Access
- Endogenous Cannabinoid System; Withdrawal Syndrome
- Genetics – match response to genotypes
- Improve / Impulsivity / Decision Making / Brain Function
- Innovative Incentive Programs
- Target Concurrent Tobacco Use
- Target Sleep
- Target Non-responders
- Innovative Use of Technology



(Lee et al., 2019, 2016, 2015)

CUD and Tobacco Use

Tobacco Users = Poorer Outcomes

engagement, impact on cannabis and tobacco

Simultaneous vs. Sequential Approach (RCT)

Phase 1 (Weeks 1-12):

Condition A: cMET/CBT/CM for CUD + Tobacco Intervention (cBT + NRT)

Condition B: cMET/CBT/CM for CUD

Phase 2 (Weeks 12-24):

Condition A: continued access to modules

Condition B: TI + continued access to modules

	SIM n=34	SEQ n=33
<u>RETENTION / ENGAGEMENT</u>		
Completed 12-wk FU	65%	67%
# Cannabis Modules complete	4.7 (3.3)	5.3 (3.2)
Tobacco Modules >1	62%	---
NRT Initiated	41%	18%**
<u>CANNABIS</u>		
% \geq 1 week of abstinence	21%	36%
Wks of Cont. Abst. (those \geq 1 Wk)	5.9 (4.0)	6.1 (3.7)
>50% reduction in days of use	27%	45%
<u>TOBACCO</u>		
Tob Quit Attempts	50%	39%
# Quit Attempts (> 0)	2.2 (1.4)	2.5 (1.9)
% >50% reduction days used	24%	21%
Point Prevalence Abst (wk 12)	18%	9%

How to Improve Outcomes?

- (1) Risky/Unhealthy Decision Making (mechanism)
Impulsivity, future orientation, self-regulation (delay discounting)
- (2) Adherence / Engagement (strategy):
Technology, Incentives

Temporal (Delayed) Discounting

- Pathological Reward Processing
- Excessively Devalue Future Rewards
- Increases Value of Immediate Rewards

More you discount the future, the more susceptible you are to the reinforcing effects of substances and impulsive-decision making

“Novel” Interventions to Target TD/FO/I

Working Memory Training (Bickel et al.; Stanger et al.)

- enhance brain function related to future-oriented decisions

Episodic Future Thinking (Epstein et al., Daniel et al., Murphy et al.)

- focus on future may increase awareness, cognizance, or consideration of delayed consequences/rewards

Priming (Sheffer et al., 2016)

- priming with future-oriented words, can reduce TD

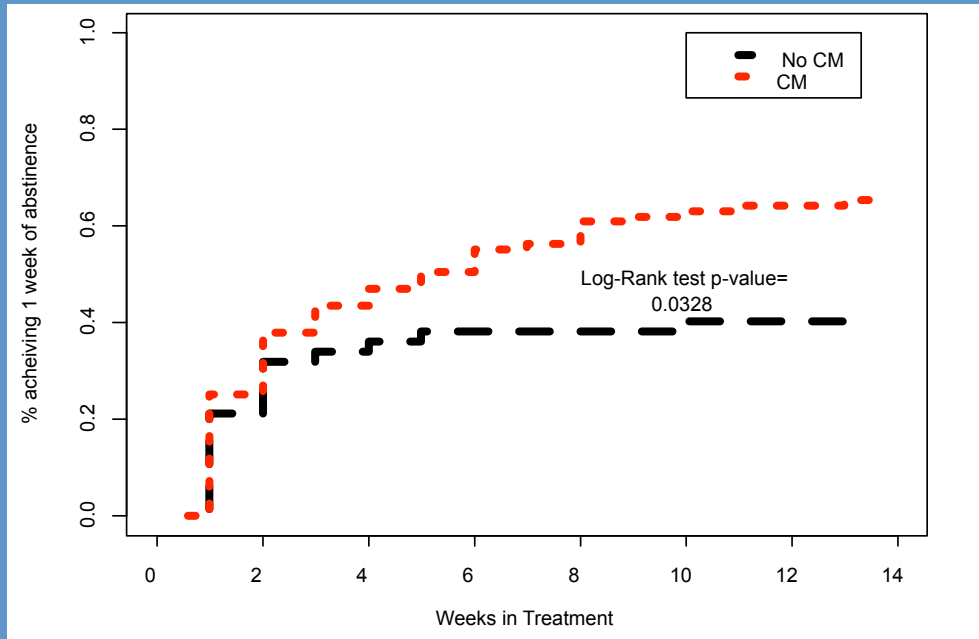
Acceptance Therapy / Mindfulness (Morrison et al. 2014)

- tolerate distress from waiting for delayed rewards

Inhibition training (Valls-Serrano, 2016; Stevens, 2015; Verbruggen, 2013, Veling, 2014)

- stop signal / go/no-go tasks, multi-tasking, maintain attention

Nonresponders: Abstinence Either Early in Trt or Not at All



Achieve abstinence by week 4-6 or
not at all. (Brown et al., 2012)

Delay Discounting Predicts Abstinence Outcomes

DD of \$1000 predicted achieving:

- ≥ 4 of abstinence: OR= .87 [.77, .99]
- ≥ 8 of abstinence: OR= .82 [.71, .95]

**** controlling for treatment condition**

Delay discounting of \$1,000 predicted during
treatment abstinence over and above the effects
of type of treatment received. (Stanger et al., 2012)

Teens: Time to get SMART

Sequential Multiple Assignment Randomized Trial

Youth: Inner City Baltimore Treatment Clinic

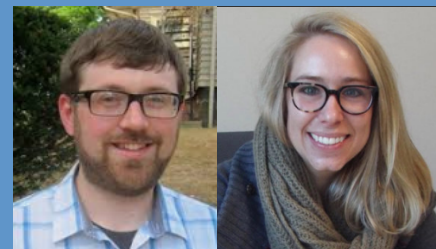
Stanger et al., in press

(1) Test a new add-on First Line intervention:

- Improve executive functioning / impulsive decision-making with working memory training – based on DD predicts outcomes in prior studies (Stanger et al., 2012)

(2) Adaptive CM for Treatment for Nonresponders:

- **Increase the magnitude (3x) of CM incentives** for those who are still using substances at Week 4



SMART Trial

Timeline

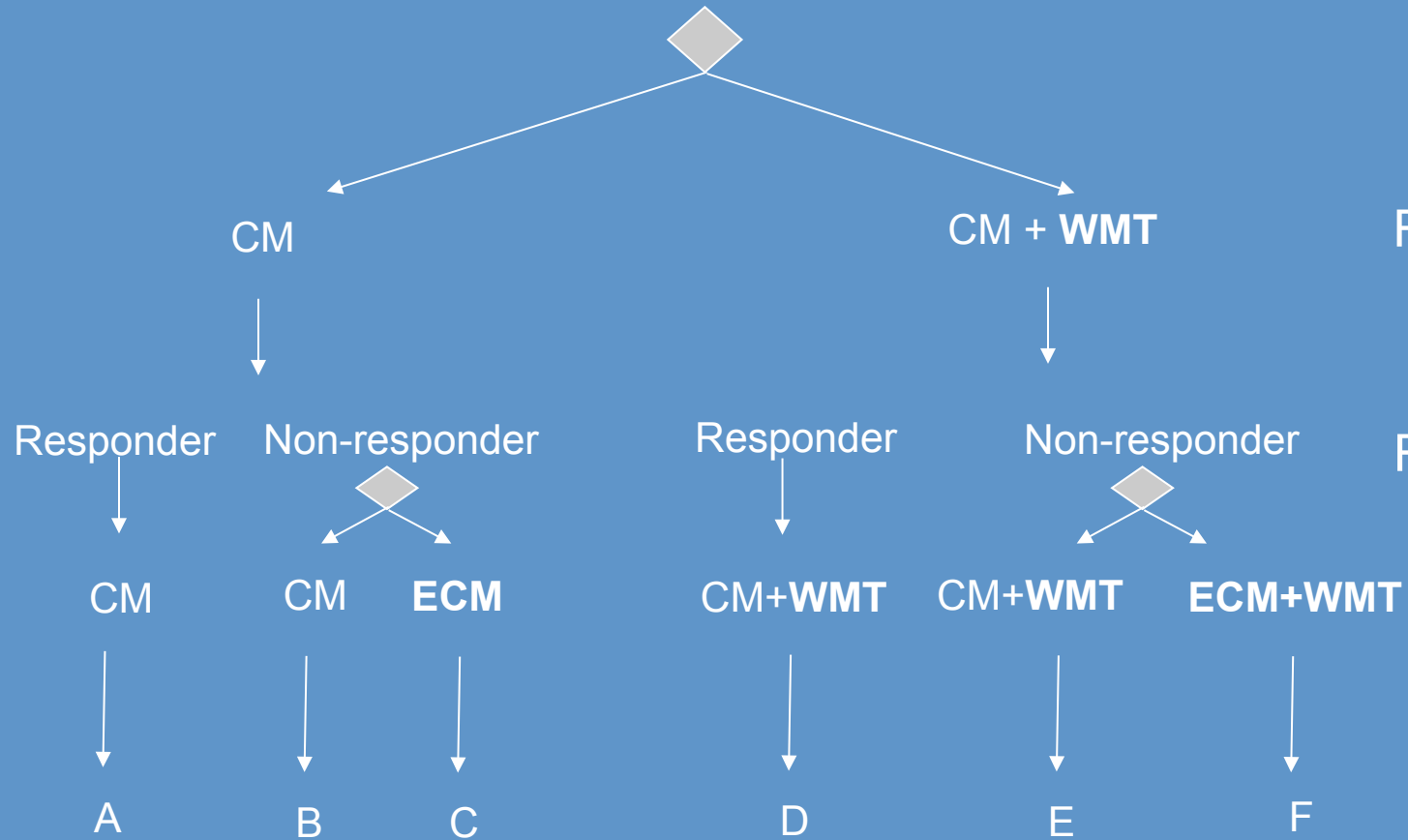
Intake

Randomize

Re-Randomize Early
Nonresponders

Phase 1:
4 weeks

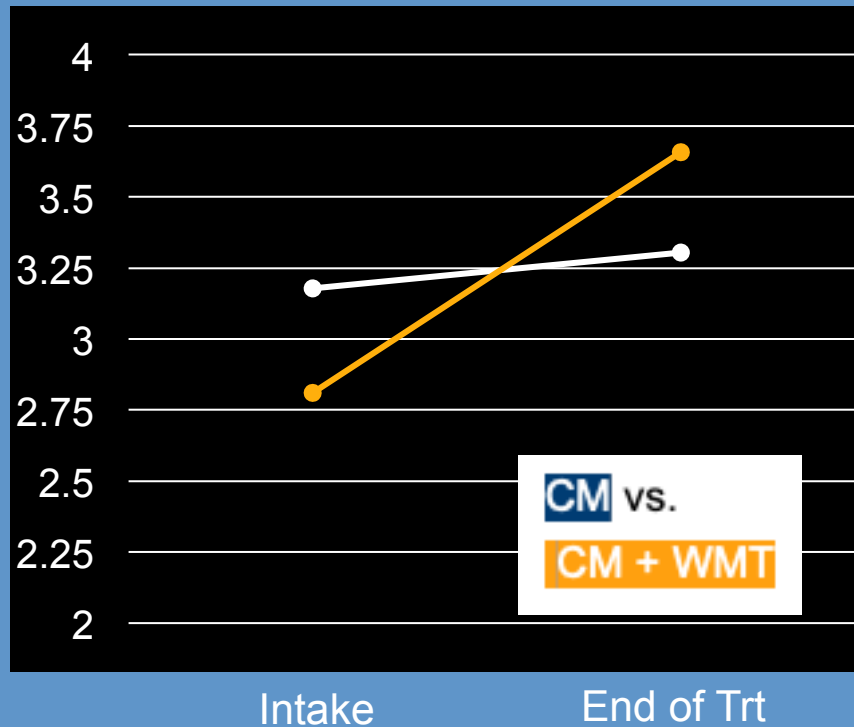
Phase 2:
10 weeks



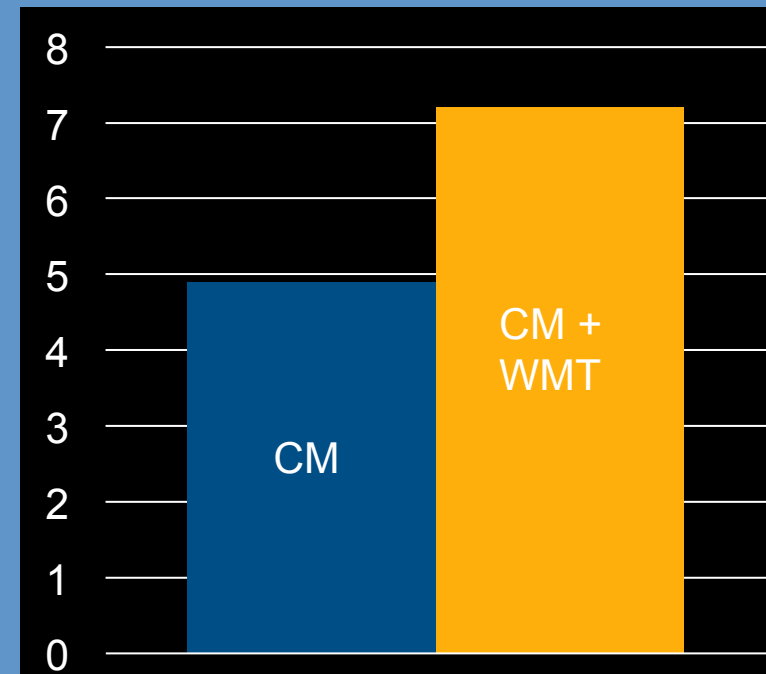
Youth SMART Trial

Youth: Inner City Baltimore Treatment Clinic

WMT changed Visual Spatial WM



WMT ↑ abstinence among those who achieved any abstinence



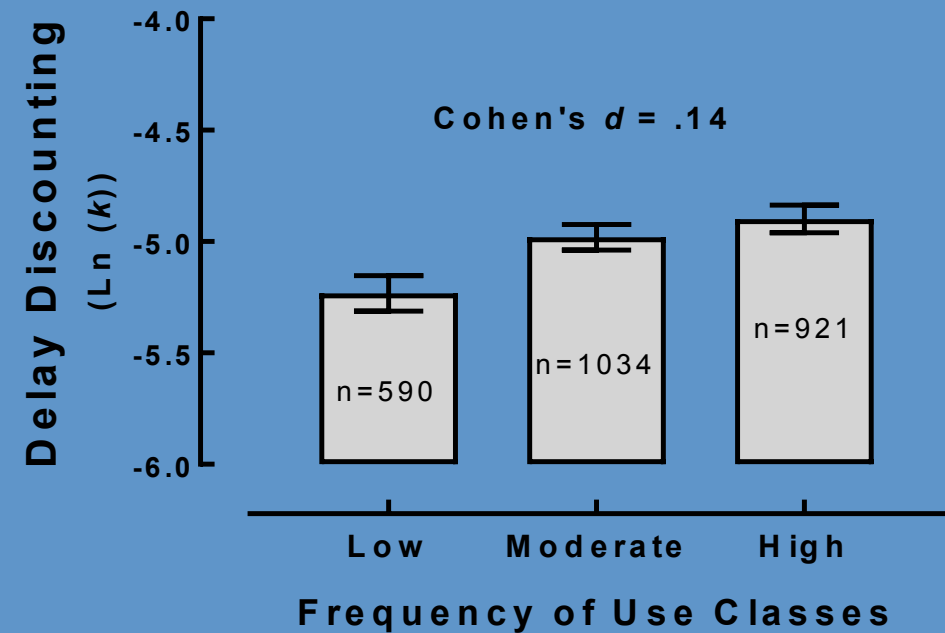
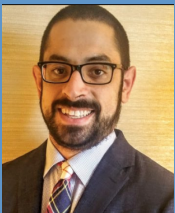
- (1) Amount of Change in WM predicted the amount of Abstinence
- (2) Increasing the Incentive Magnitude did not Work

Current Active Clinical Cannabis Research

Cannabis and Temporal Discounting (DD)

- Cannabis and DD
 - DD positive relationship with cannabis use (*Aston et al., 2016; Lopez-Vergara et al., 2019; Sofis et al., 2020; VanderBroek et al., 2013*)
 - Associated with worse cannabis treatment outcomes in teens (*Stanger et al., 2012*)
 - Treatment target for CUD or cannabis misuse

Cannabis Use Related to DD in Online (Facebook) Sample of Regular Users (*Sofis et al., 2019*)



Episodic Future Thinking (EFT) to Enhance Valuation of the Future

EFT guides creation of hypothetical, personal future events which putatively enhance attention to and valuation of the future

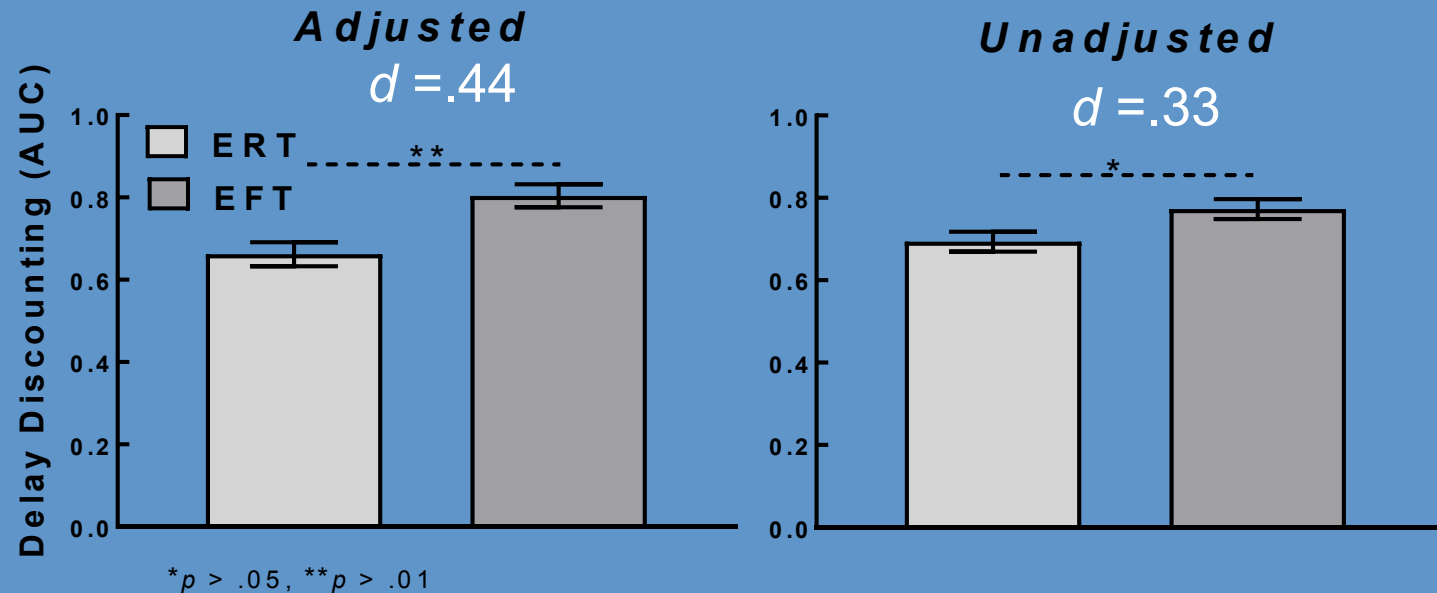
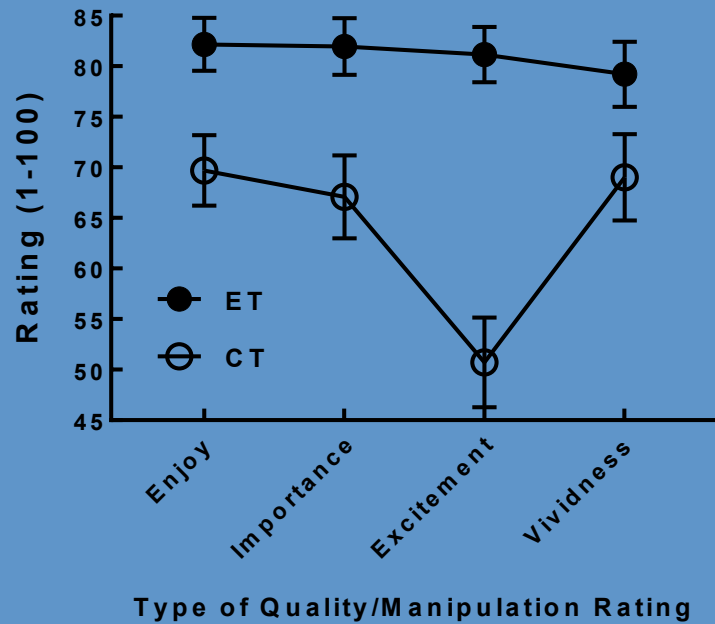
- Reduces DD in nicotine and alcohol users, obese persons (Bulley & Gullo, 2017; Snider et al., 2016; Stein et al., 2016; Stein et al., 2015)
 - Reduced DD mediated the relationship between EFT and reduced substance use (Chiou & Wu, 2017)
- No research on the effects of EFT on cannabis users

Initial Study: Single Online EFT Session decreases DD

Sofis et al., in press

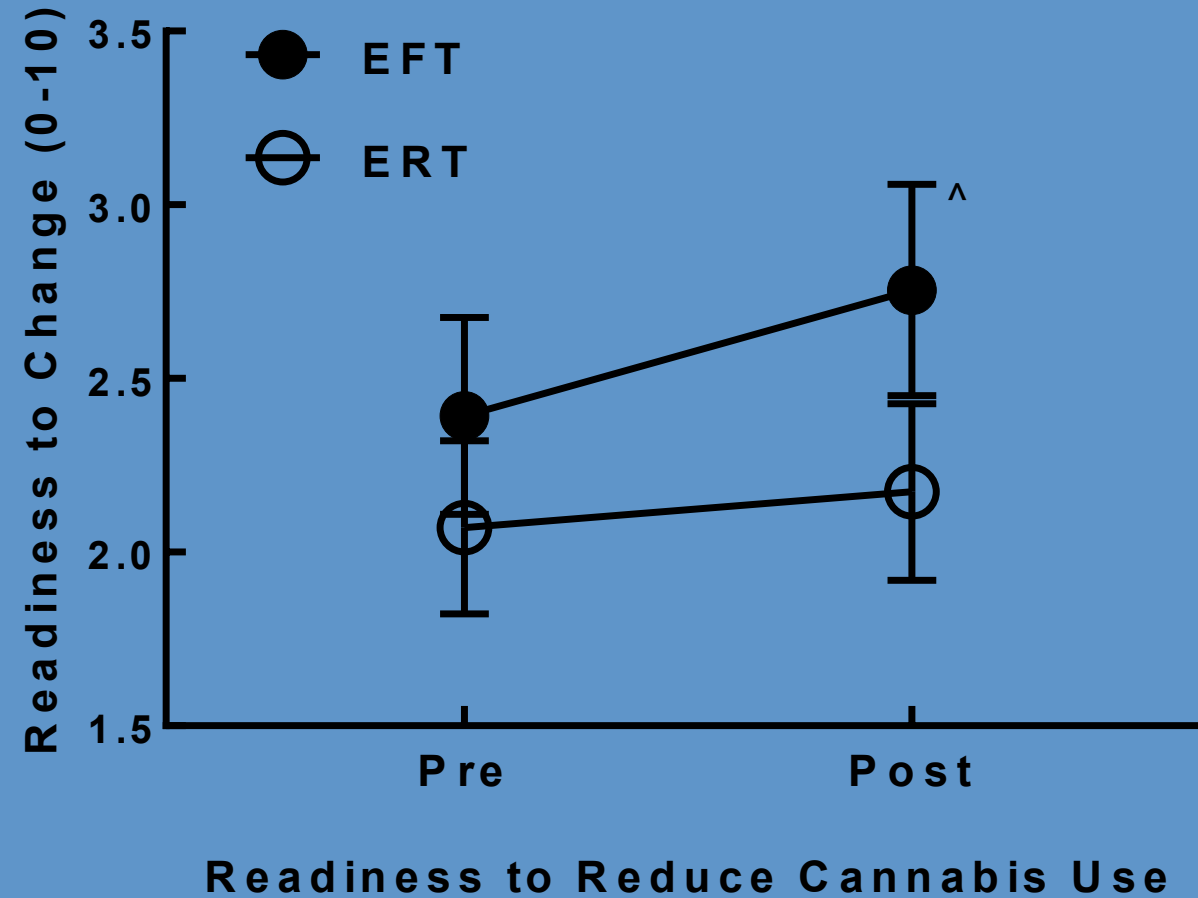
- Cannabis users recruited from mTurk (n=200, 44% **with** CUD)
 - **Event-creation prompt:** *“Think about the most positive event that could realistically happen for you 1 day from now. Describe this event”*
 - *“What will you be doing? Who will you be with? Where will you be? What will you be feeling?”*
- Randomized Between-Group Design
 - **EFT:** Events 1 day, 1 week, 1 month, 3 months, 1 year
 - **Control EFT:** Events yesterday 7-10 pm, 4-7 pm, 1-4 pm, 10-1 pm, 7-10 am
- Measures:
 - Event manipulation check ratings (enjoyment, importance, vividness, excitement)
 - DD (post-EFT); Readiness to change cannabis use (pre/post EFT)

EFT Associated With Better Event Ratings, Reduced DD Relative to ERT



Adjusted model controlled for demographics, quality/manipulating ratings, substance use (cannabis, alcohol, tobacco, and illicit opioids), CUD status, and time perception.

EFT may increase Readiness to Change Cannabis Use



[^] $p = .069$

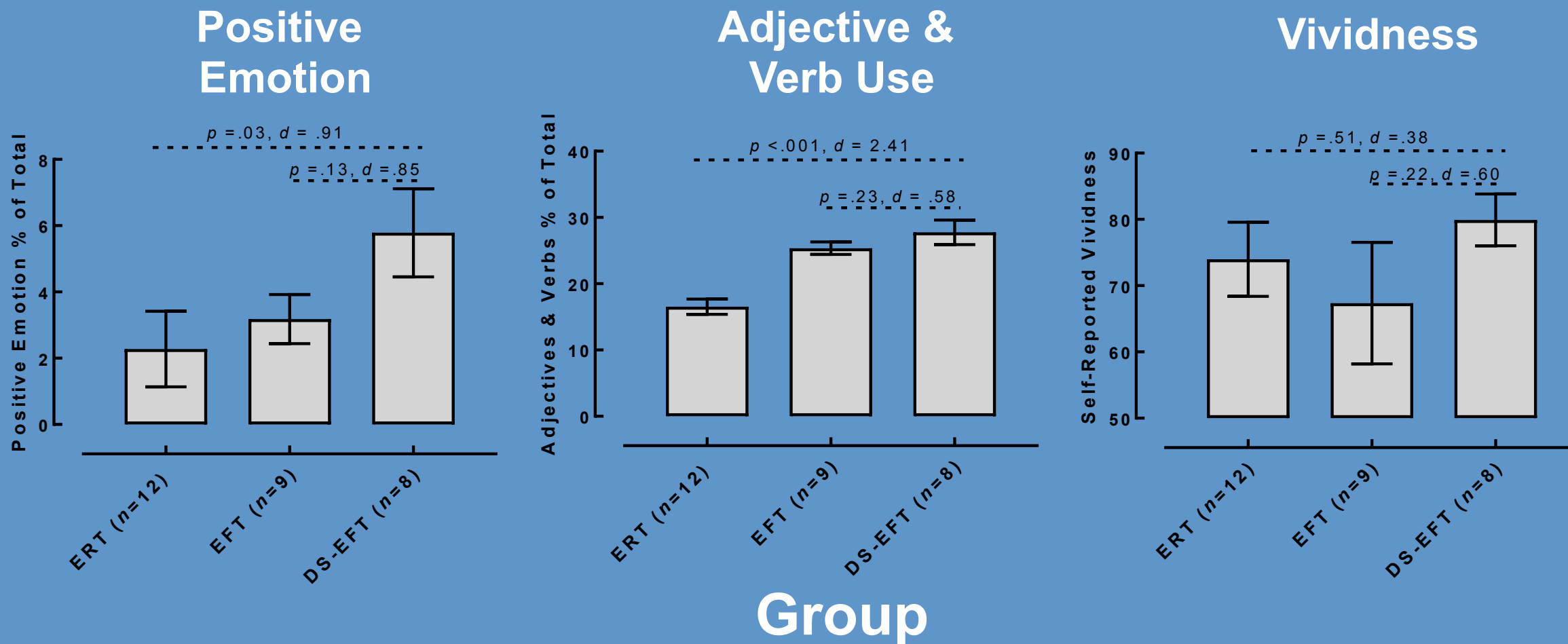
Study 2: Effects of Domain-Specific EFT on DD and Cannabis Use *(In Progress)*

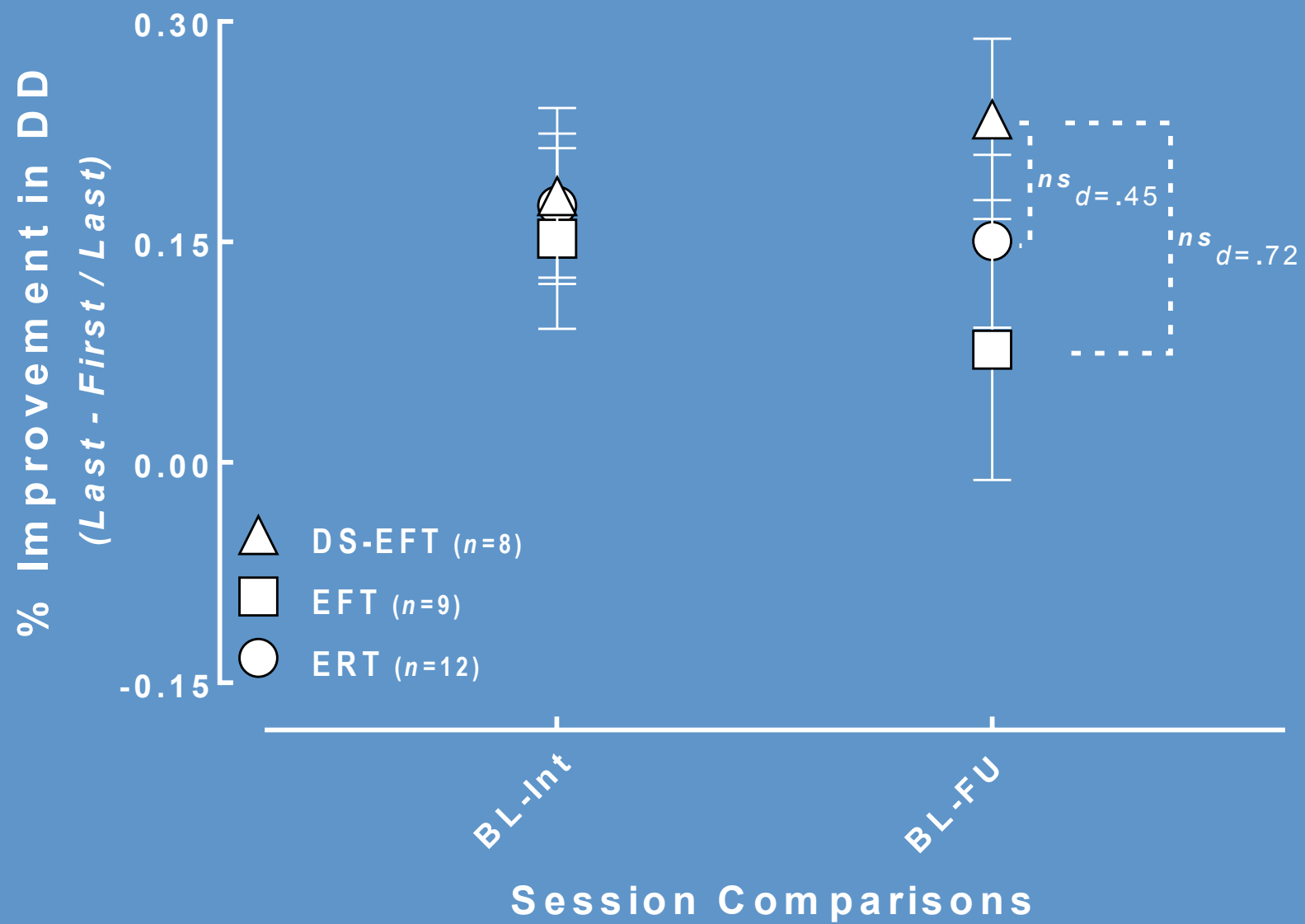
- Three main questions
 - Can we enhance impact on DD by making future events more positive and salient?
 - Will an enhanced EFT show greater reductions in DD than typical EFT and ERT?
 - Will an enhanced EFT show reductions in cannabis use?
- Cannabis use negatively impacts episodic memory
 - May constrict creation, attention, and valuation of future events
 - May help to use EFT across life domains (i.e., domain-specific EFT; DS-EFT)
 - DS-EFT (*Leisure, Social, Health, Career/financial*)

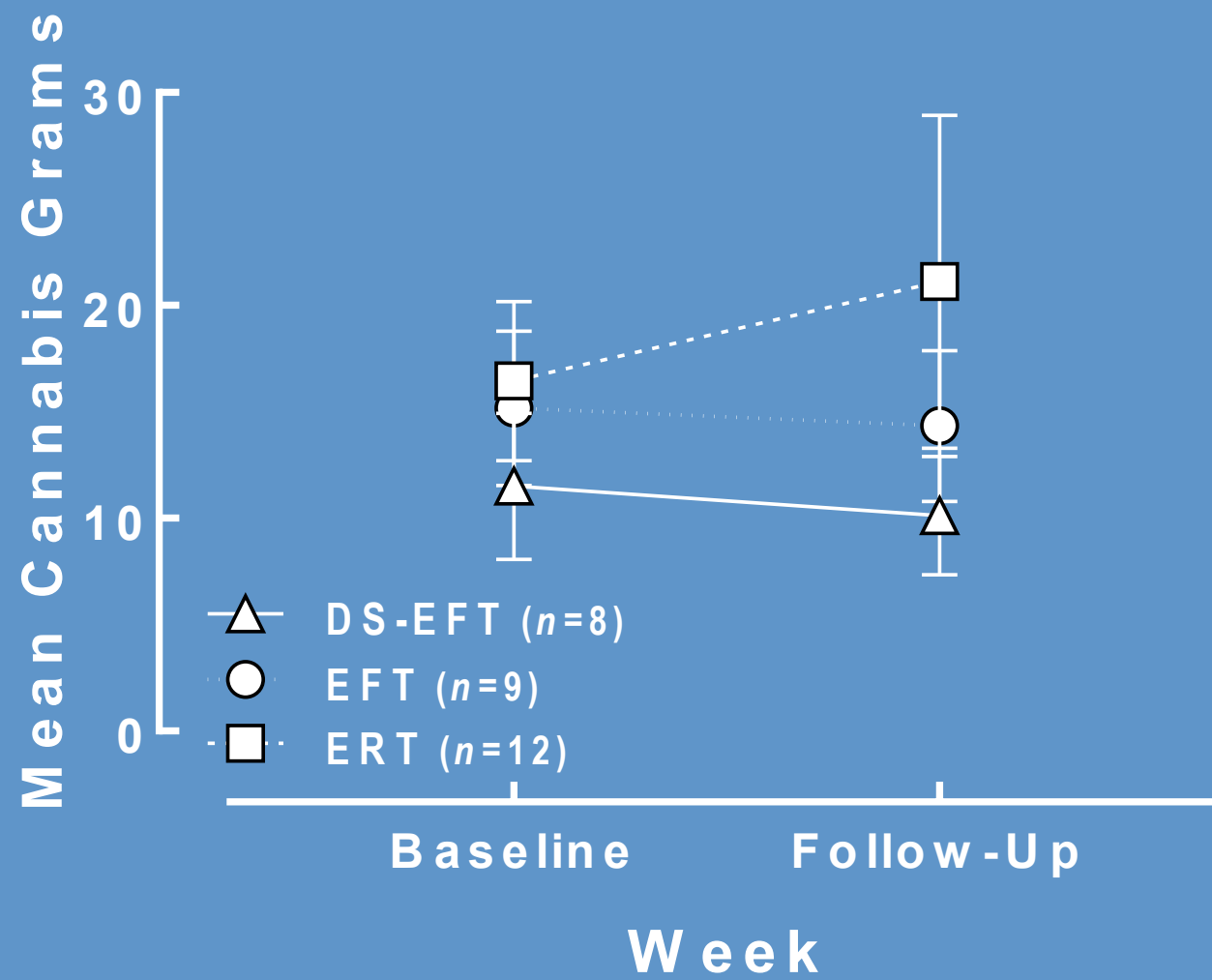
Study 2: Effects of Domain-Specific EFT on DD and Cannabis Use *(In Progress)*

- Participants: Cannabis users from mTurk for 3-sessions ($n=36$, 44% CUD)
 - Baseline (*Day 1*), TLFB grams and instances of cannabis, DD
 - Intervention (*Days 2-4*), event quality/manipulation ratings, DD
 - 1- week Follow-up (*Days 9-13*), TLFB grams and instances of cannabis, DD
- Intervention: *Randomized to ERT, EFT, or DS-EFT*
- Measures:
 - Event quality/manipulation ratings (vivid and realistic)
 - DD
 - Cannabis Use Frequency, Grams of Use
 - Linguistic analyses of created events tested whether DS-EFT events are more salient, positive

Manipulation Check / DS-EFT Enhances Process?







Tentative Study 3 Plan: Multiple EFT Sessions to reduce Cannabis Use

Test repeated sessions of DS-EFT in Study 3

Cannabis users interested in change **recruited from Facebook (~ clinical sample)**

RCT: DS-EFT vs. ERT

6 weekly sessions

Follow-Up assessment

Prevention: Public Perception

What's the Problem?

Legalization and government-approved medical indications for cannabis influence:

Public Perception, Behavior, Availability

...which increases the probability of developing problems related to cannabis use?

Perceived Risks and Benefits?
Wellness Classes: UVM College Freshman and Sophomores
(n > 1000)

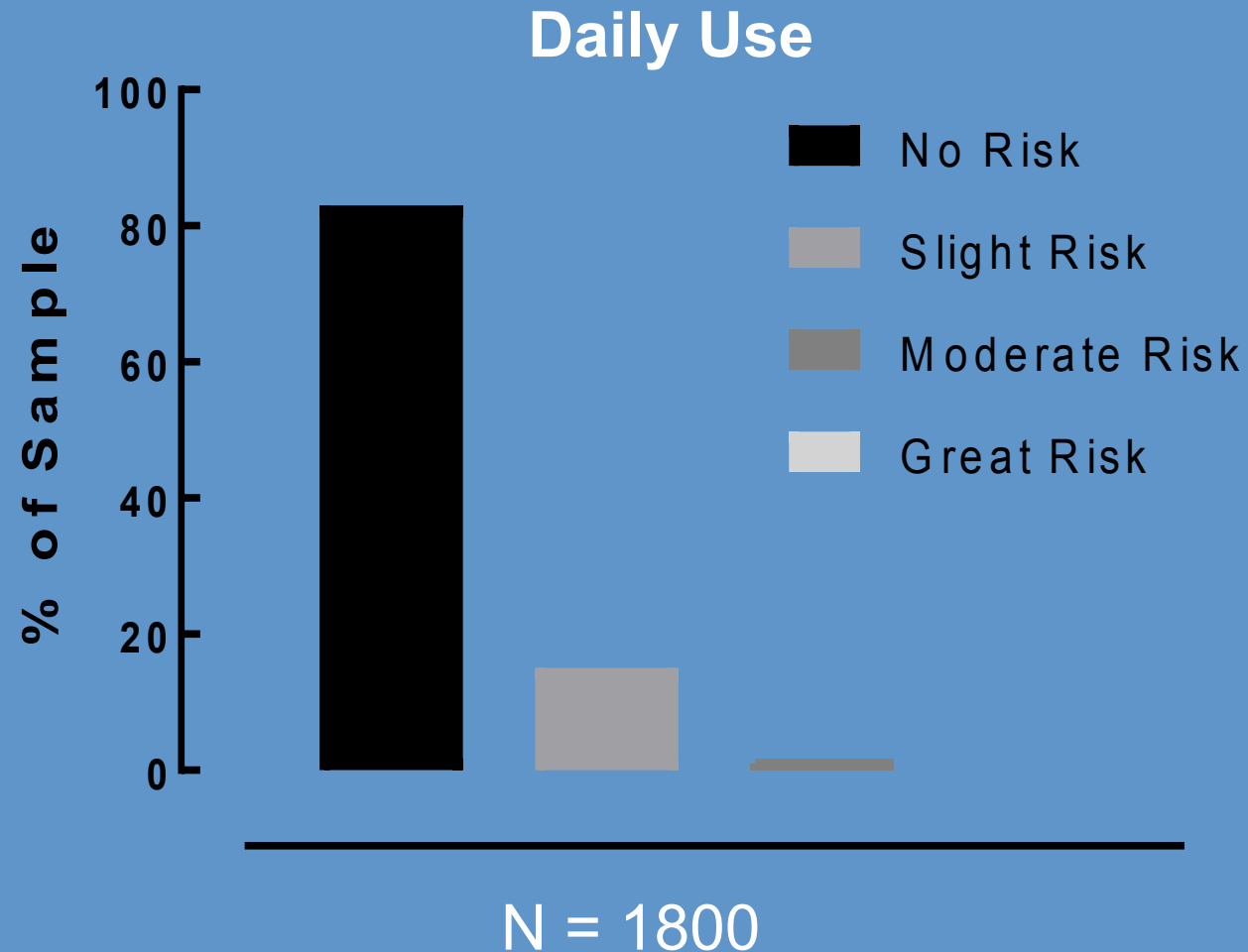
Cannabis has therapeutic benefit for:

Depression	Yes	79%
Anxiety	Yes	71%
ADHD	Yes	43%
PTSD	Yes	76%
Pain	Yes	88%
Can Quit Easily	Yes	50-59%

(2018)

Traditional Risk Perception Measure

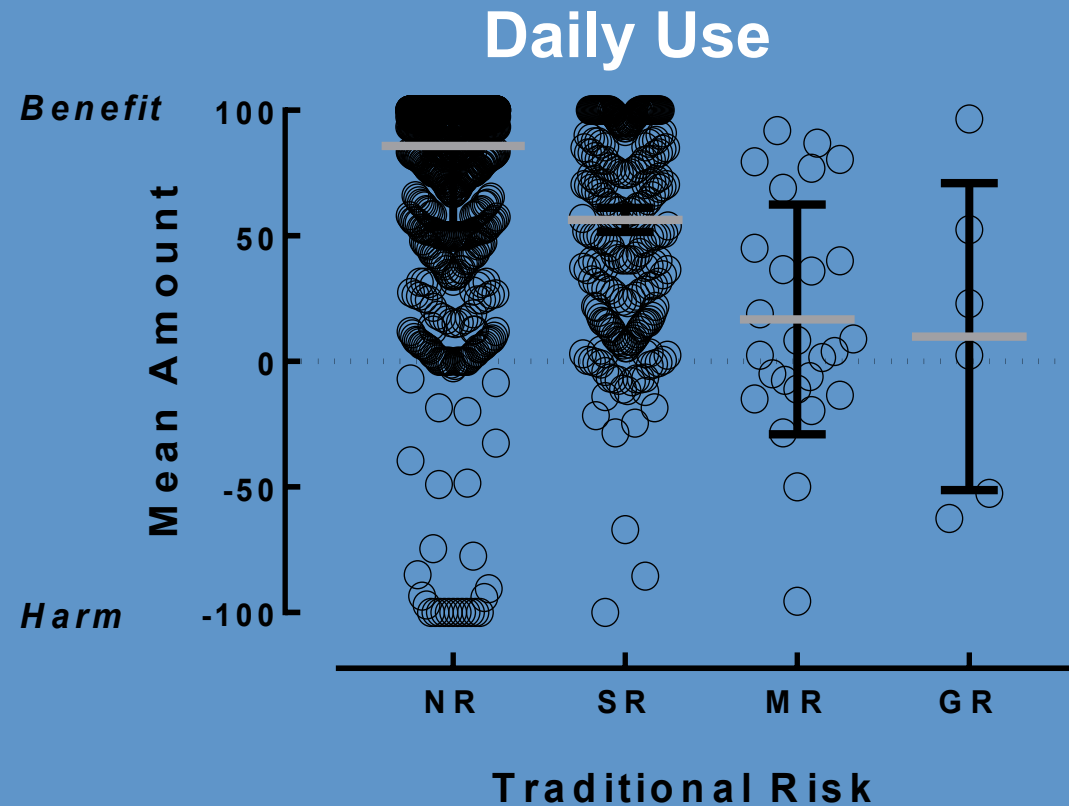
How much do you think people risk harming themselves (physically or in other ways) if they smoke marijuana regularly



Novel Risk Perception Measure

VAS: 100 to -100 (Benefit to Harm)

What is the likelihood of physical harm or benefit using mj daily or almost daily?



Note: grey lines denote means and black lines 95% CIs

Future / Pending Projects

Digital Epidemiological Survey to Determine Low vs. High Risk Patterns of Cannabis Use

Unlike for Alcohol, we are clueless about:

- How much or what patterns of use are safe/low risk?
- How do we quantify use / define patterns?
- How do we define meaningful change (outcome measures)

*** Pending NIDA application**

N = 15,000 cannabis users

Ubiquitous Need for This Information

Epidemiologists and economists: impact of cannabis laws, attitudes and markets, and to determine the risks of consequences by level of cannabis exposure and individual characteristics.

Clinical researchers: a sensitive index as an outcome in clinical trials - other than abstinence

Clinicians: information to guide treatment and advise patients about safe levels of use.

Health educators and policy makers: to plan intervention and prevention programs, to design regulatory provisions, and to provide accurate information about cannabis risk to the public

Public Health Challenges

- 1) De-Medicalize Cannabis Use (THC-laden)
- 2) Change Positive Public Perception
- 3) Adopt Harm Reduction Perspective and Policies
- 4) Impact of Burgeoning Industry

Addictive and Therapeutic?

Not Unique

Opioids

Cocaine

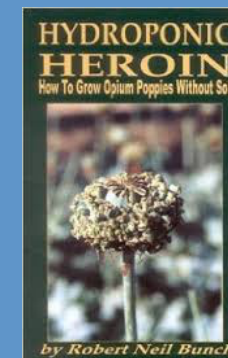
Tobacco

Stimulants / Amphetamines

Alcohol

Hallucinogens

Can make public health messaging most difficult!



Cannabis Industry Impact

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



CANNABIS AT UVM

COURSES

Cannabis Science and Medicine Professional Certificate
Professional Certificate in Cannabis Plant Biology

UVM is the first medical school in the nation to offer a professional certificate in cannabis and medicine. Our seven-week, online professional certificate is designed for physicians, dispensary personnel, nurse practitioners, pharmacists, physician assistants, and regulators.

As a new industry-leading credential UVM's Professional Certificate in Cannabis Science and Medicine gives professionals assurance they can accurately inform patients and customers, as well as gain a competitive advantage as a knowledgeable, trustworthy provider who can effectively minimize the risks and maximize the benefits of cannabis for therapeutic use.

What We Know

- Cannabis (Marijuana) Use Disorder is real and impacts a substantial number of teens and adults
- Many teens and adults enter treatment for CUD
- Interventions that help have been developed, but many do not respond and many relapse
- Increased availability of high potency (THC) marijuana products combined with the rapid growth of for profit marijuana industry will ↑ CUD and related problems

Cannabis Research Priorities

- Better translate knowledge into more effective prevention/treatment
- Protect and Treat Populations Vulnerable to Addiction
 - disadvantaged/poor, mental and physical health disorders, youth
- Communication Science: risk and benefits
- Develop Cannabis Use Guidelines
 - What level of use is low risk? high risk?
 - Help people make informed and safe choices
- Regulatory Science: mitigate harm
 - Industry/marketing, dose/content control, access

Science is a Slow Process



Contributors / Thanks

Faculty/Trainees

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Jody Kamon

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- R01-DA015186 (Behavioral Treatments for Adolescent Cannabis Use)
- R01-DA023526 (Development of Computerized Treatment for Marijuana Use Disorders)
- U01-DA031784 (Role of Sleep in the Treatment of Cannabis)
- Copy of Slides, Articles, or Other:

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State politicians / Legislatures have informed the public that “Marijuana/Cannabis” is a medicine that is effective with a host of disorders

Those dispensing / selling / promoting these products (cannabis industry) inform the public / consumer which compounds are effective for what condition, provide “education”, recommendations, and sell the product

Physicians / Medical Societies generally do not support Medical Marijuana Laws, although some would support Legalization with Regulation

Booming Cannabis Industry looking to profit!

Acknowledgments and Disclosures

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NIH-NIDA

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P30-DA029926 Center for Technology & Behavioral Health (Marsch, PI)

Cannabis as Reinforcer

Cannabis Use Disorder / “Addiction”

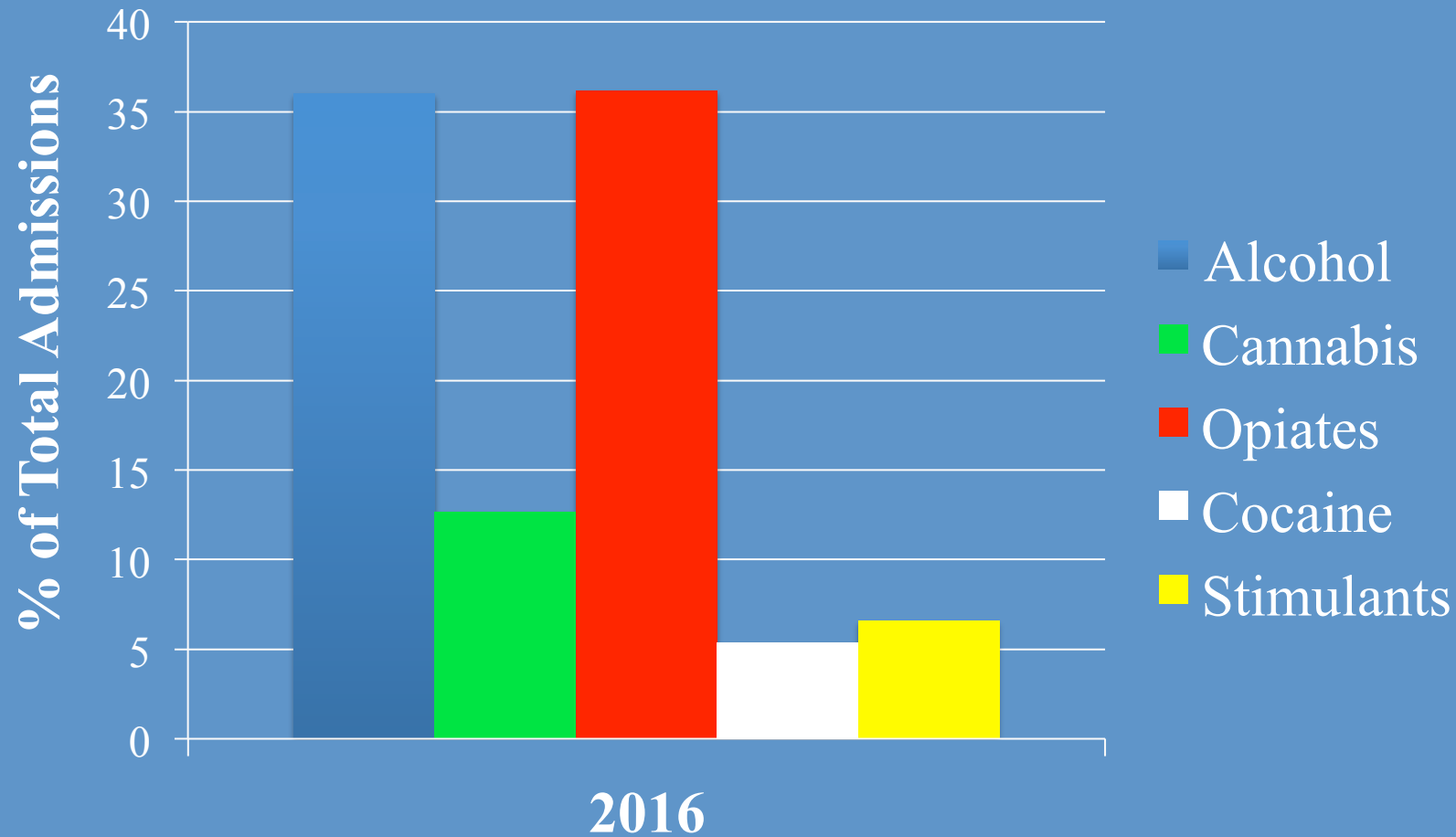
https://www.youtube.com/watch?v=o4W6cS_9xxk

CUD Past Year Prevalence: NSDUH (2018)

<u>AGE</u>	<u>% with CUD</u>	<u>ALCOHOL</u>
12 and older	1.6%	5.7
12-17	2.1%	5.4%
18 and older	1.6%	5.8%
18-25	5.9%	10.1%
26 and older	0.9%	5.1%

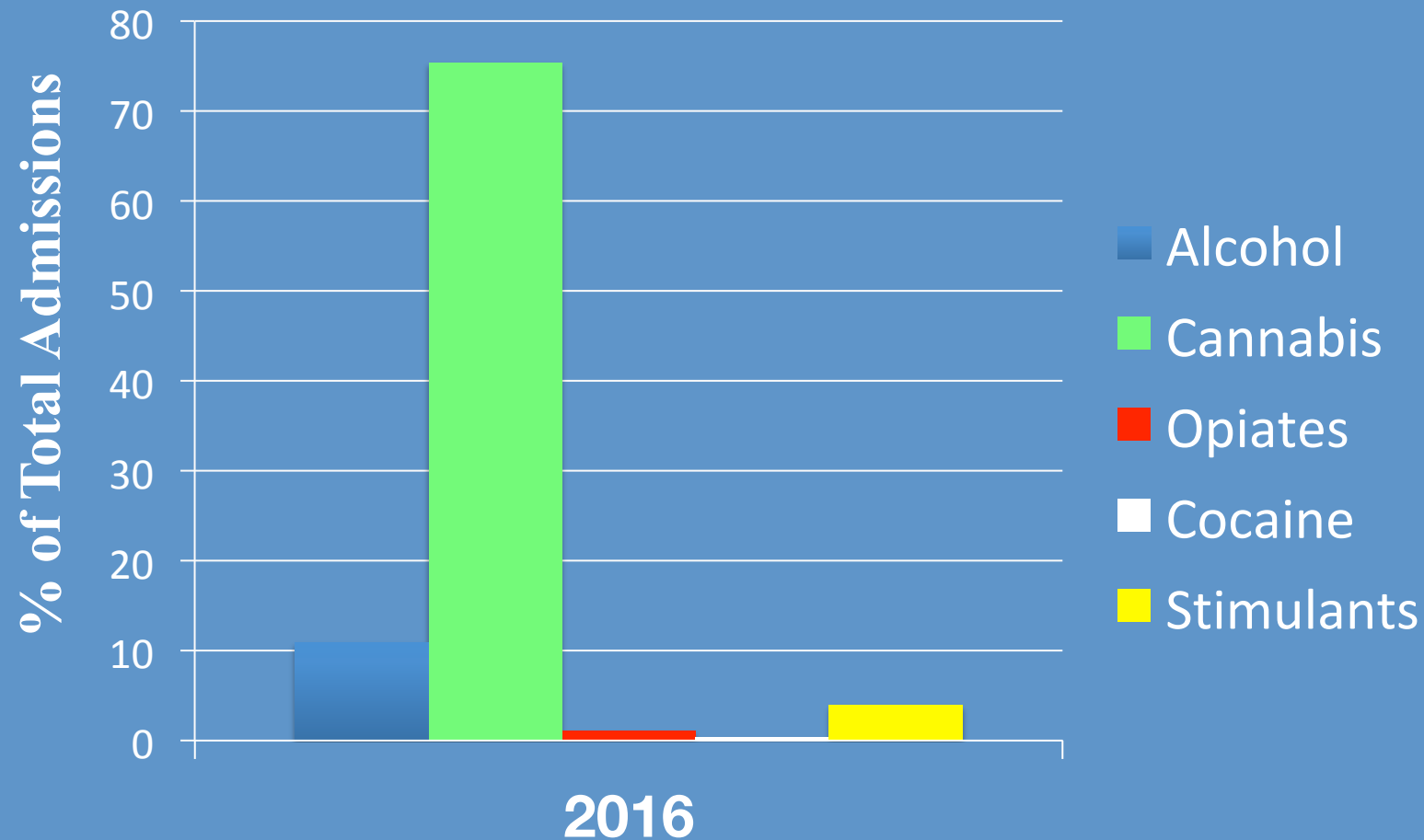
U.S. Treatment Admissions Primary Substance

TEDS Data (age 12 and above)



US Treatment Admissions Primary Substance

TEDS Data (12-17 years)



Continued Treatment Development Challenges

- 1) Non-responders / Improve initial treatment response
- 2) Maintenance of effects
- 3) ** Reduced use / Harm reduction (meaningful outcome indices)
- 4) Schedules of Reinforcement (Incentives) / Types of Reinforcers
- 5) Integrate mHealth interventions with “mainstream treatment”
- 6) Personalize / match interventions

De-Medicalize Cannabis / Marijuana?

Age - Neurodevelopment?

- Age requirement to purchase
 - “Recreational” Cannabis: 100% of States = 21 yrs
 - “Medical” Cannabis: > 50% of States = 18 yrs
 - in California (LA) almost all stores are for both Rec and Med
 - 18 yr old can walk in and buy whatever he/she/they desire

Content of Active Compounds (THC/CBD) in Cannabis Products

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