

Cannabis Across The Lifespan: Biological Risks, Benefits and Vulnerable Populations

**Preconference Workshop on Marijuana,
North Carolina Psychiatric Association (NCPA)
Annual Conference
*September 18, 2025***

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and Mental Health

Disclosures – Tony P. George, M.D.

- **Research Funding:** CIHR, NIDA, TRDRP, CAMH Foundation
- **Co-Principal Editor,** *Neuropsychopharmacology* (NPP)
- **Advisory Boards:** University of Toronto TC3 Consortium; DSMB Chair, Yale Tobacco Regulatory Center (TCORS); Yale K12 Faculty Training Program in Addictions Research; Office of US Surgeon General; Jacob Waletzky Award Selection Committee, Society for Neuroscience (SfN)



National Institute
on Drug Abuse

Advancing Addiction Science



Canadian Institutes of Health Research
Instituts de recherche en santé du Canada



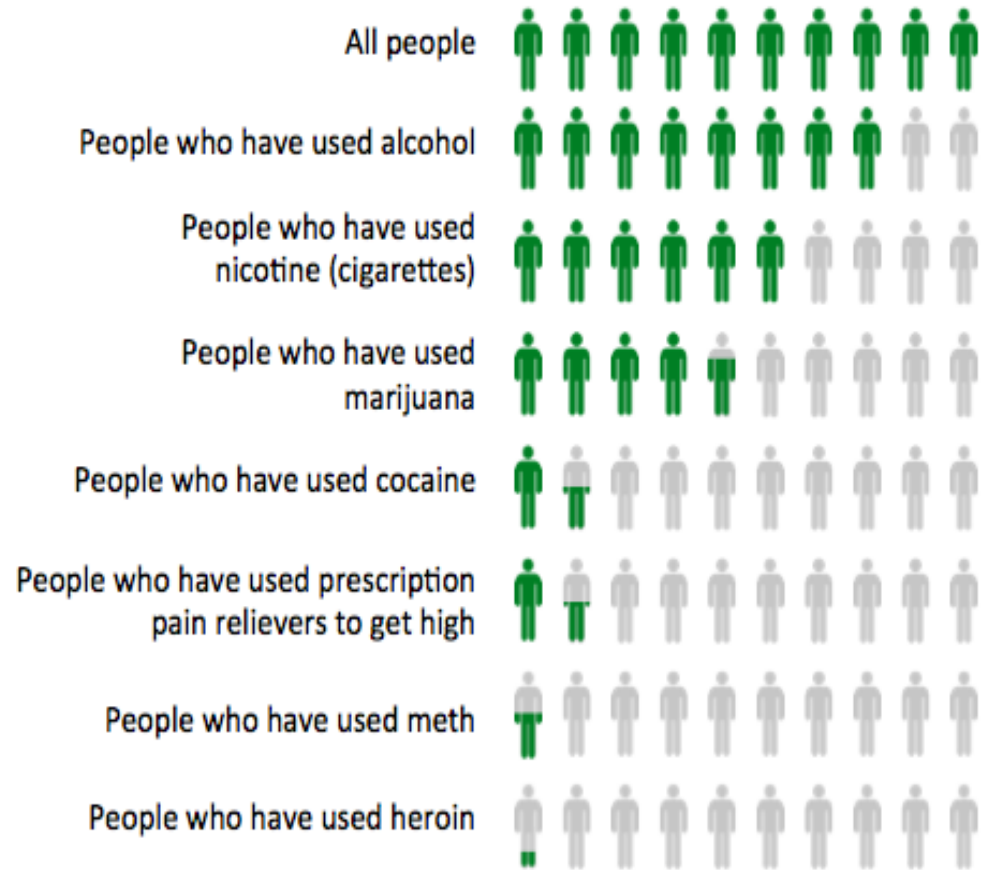
Objectives

- Describe the risks and potential benefits of cannabis in the general and vulnerable populations, across the age spectrum.
- Describe how two novel approaches (e.g. brain stimulation, contingent reinforcement) can be used to parse mechanisms that link cannabis to mental illness; and
- Apply this knowledge in the successful treatment of co-occurring cannabis addiction in people with mental illness.

Cannabis Facts - 1

- Prevalence of cannabis use disorder (CUD) is ~2.9% in U.S. general population, ~4.0% in Canada, and higher in psychiatric samples (15-30%)
- Rates of lifetime use ~45%
- Derived from *Cannabis Sativa/Indica* plants

FIGURE 1. Lifetime use of mood-altering drugs



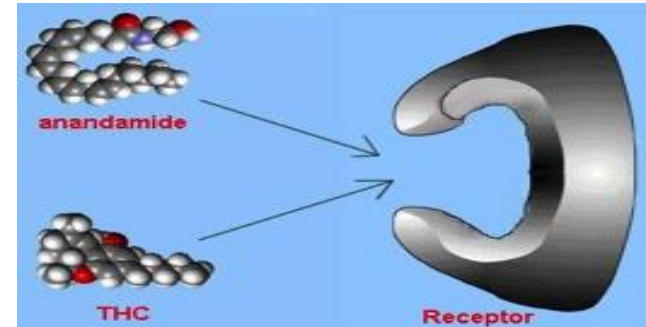
Cannabis Facts - 2

Contains over 400 compounds; 60+ cannabinoids

- Delta-9-Tetrahydrocannabinidiol (THC), Cannabidiol (CBD)

THC Pharmacology

- Acts at cannabinoid 1 receptors (CB1R)



Highly Lipophilic: Fat-soluble

- Long half-life
- Deposits in adipose tissue and re-released into blood
- Recurrent use can lead to cannabinoid accumulation (Ashton 1999)
- Metabolized into long-acting metabolites 11-OH-THC and THC-COOH
- Complete elimination may take up to one-month (Huestis, 2015; Rabin et al., 2017)

Cannabis Intoxication and Withdrawal

- There is a clear dependence and withdrawal syndrome (Vandrey et al., 2004; Sorkhou et al, 2021)
- Intoxication – cognitive impairment, psychomotor impairment, conjunctival injection, severe anxiety.
- Withdrawal – irritability, decreased appetite/weight loss, restlessness, difficulty falling asleep, depressed mood, abdominal pain sweating (peak within 4-7 days)

Is Cannabis Addictive?



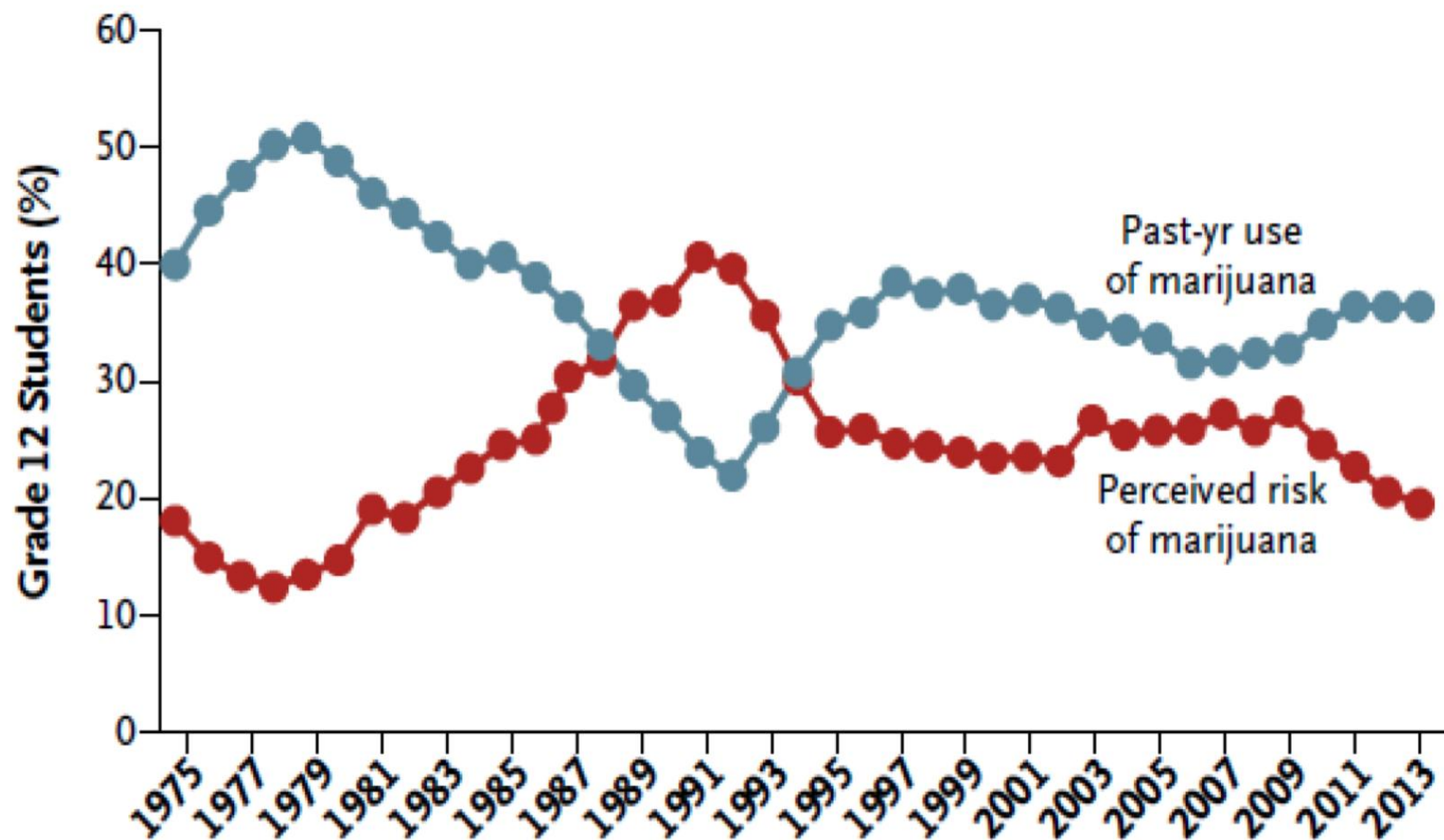
"Wish I could!"

Monitoring the Future Study (MFS) Results



Substance	Cumulative Occurrence of Drug Use (%)	Cumulative Occurrence of Drug Dependence (%)	% Capture Rate
Tobacco	75.6	24.1	31.9
Cocaine	16.2	2.7	16.7
Heroin	1.5	0.4	23.1
Alcohol	91.5	14.1	15.4
Cannabis	46.3	4.2	9.1

A Correlation between Perceived Risk and Use



From: Monitoring the Future Study (MFS); reviewed in Volkow et al., 2014. NEJM

THC versus CBD Content: 1975 and 2025

- In 1975: THC, 3%; CBD, 3%
- In 2025: THC, 25-45%; CBD <0.1%



Hasin, D.S. (2018). *Neuropsychopharmacology*. 43: 195-212.

Sorkhou, M. et al. (2021). *Front. Psychiatry*. 12: 630247

Different Routes of Cannabis Use

Smoked



Joint



Bong

Blunt



Vaporized



Vaporizer

Vape Pen



Ingested

Candy



Baked Goods



Artisanal



Oh, Canada!



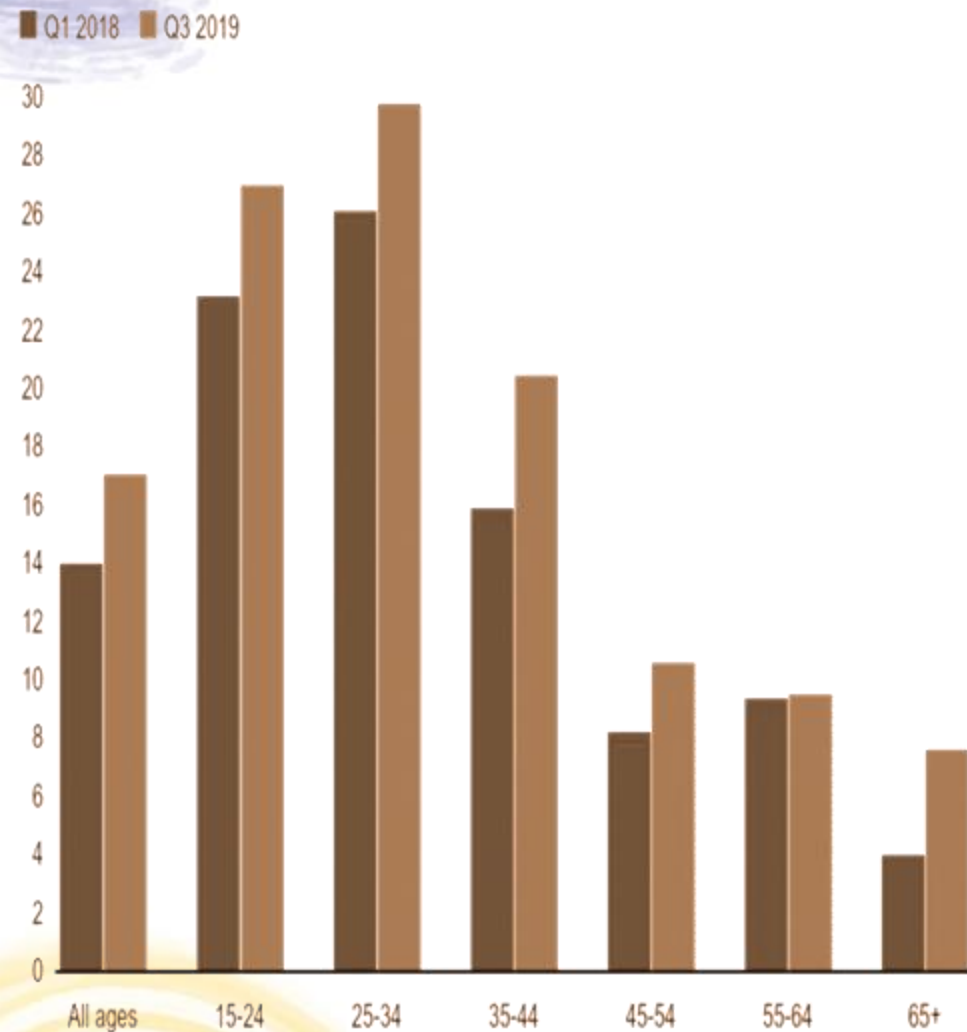
Recommendations of Canada's Cannabis Legalization Working Group (Ware et al., 2017)

- Legal access 19 years and above (*Alberta is 18 and Quebec is 21 years*)
- 30 grams personal possession dried cannabis
- 4 plants per household
- Clear Labeling of THC and CBD content
- Vaporizers and Edibles
- Strict regulation on commercial production with quality control.
- Progressive penalties for violations
- **Legalization began October 17, 2018**
(Bill C-45, the Canadian Cannabis Act)



Cannabis Use in Canada

Cannabis use by age, self reported

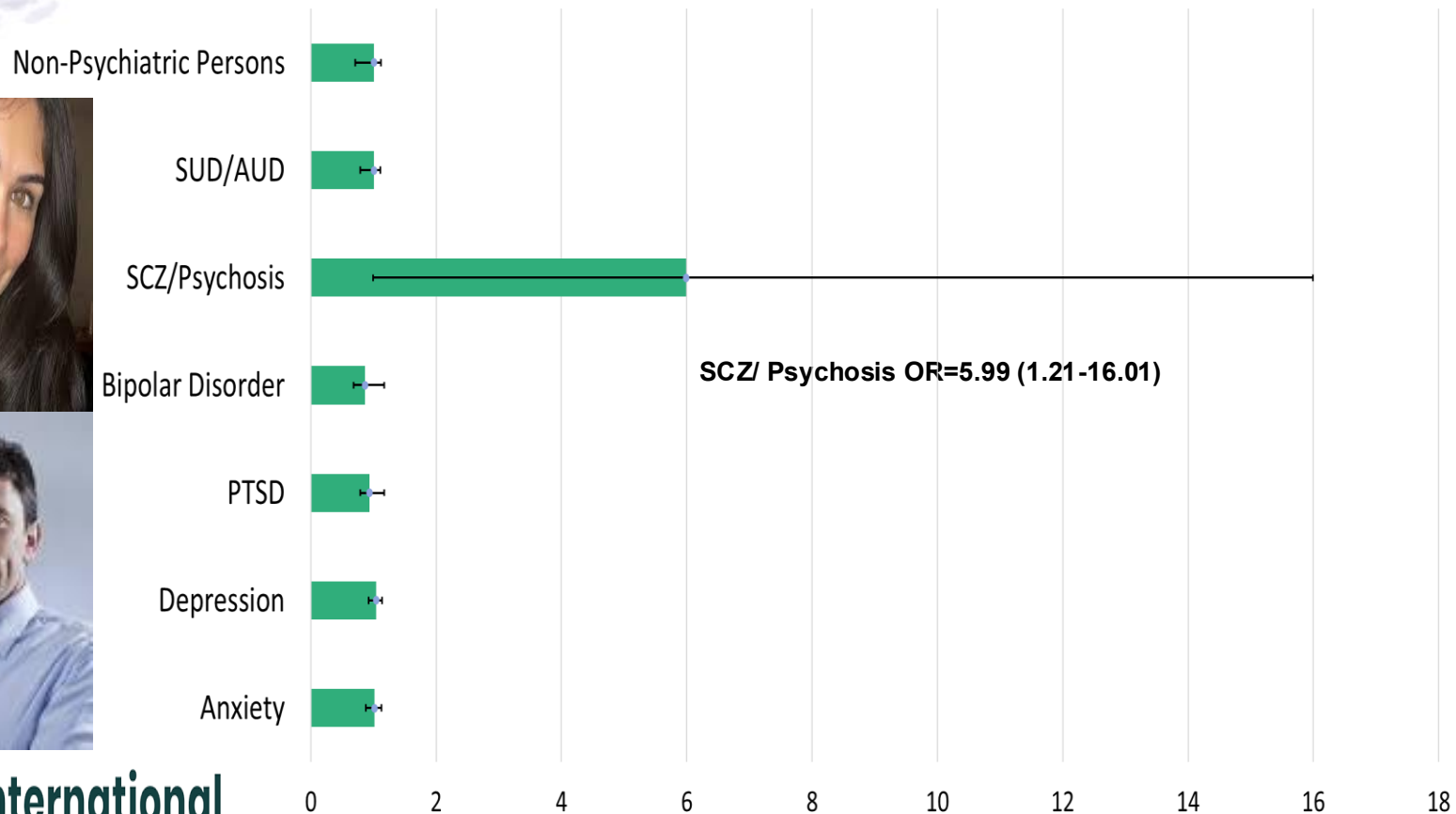


Since the legalization of recreational cannabis use in October 2018, rates of cannabis use have increased^(Statistics Canada, 2020).

This increase in use may be of concern to vulnerable populations, including youth, and people with Mood and Anxiety Disorders, and Psychosis.

Odds Ratios for Increases in Daily Cannabis Use After Canadian Cannabis Legalization (2018-2020)

Odds Ratios of Being a Daily Cannabis User Pre- to Post-Legalization Among Canadian Cannabis Users Reporting 12-Month Psychiatric Symptoms



Cannabis Legalization and Psychiatric Disorders: Caveat “Hemp-tor”

The Canadian Journal of Psychiatry /
La Revue Canadienne de Psychiatrie
2018, Vol. 63(7) 447-450

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DOI: 10.1177/0706743718762387

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Keywords

cannabis, mental illness, drug policy, legalization, addiction, psychiatry



LEGALIZING MARIJUANA 'ONE OF THE BIGGEST MISTAKES OF ALL TIME.'

"I maintain that it's addictive. It leads to other drugs," John said. "And when you're stoned — and I've been stoned — you don't think normally. Legalizing marijuana in America and Canada is one of the greatest mistakes of all time."

~ Sir Elton John



DISPENSING

TRUTH

EVERY BRAIN MATTERS

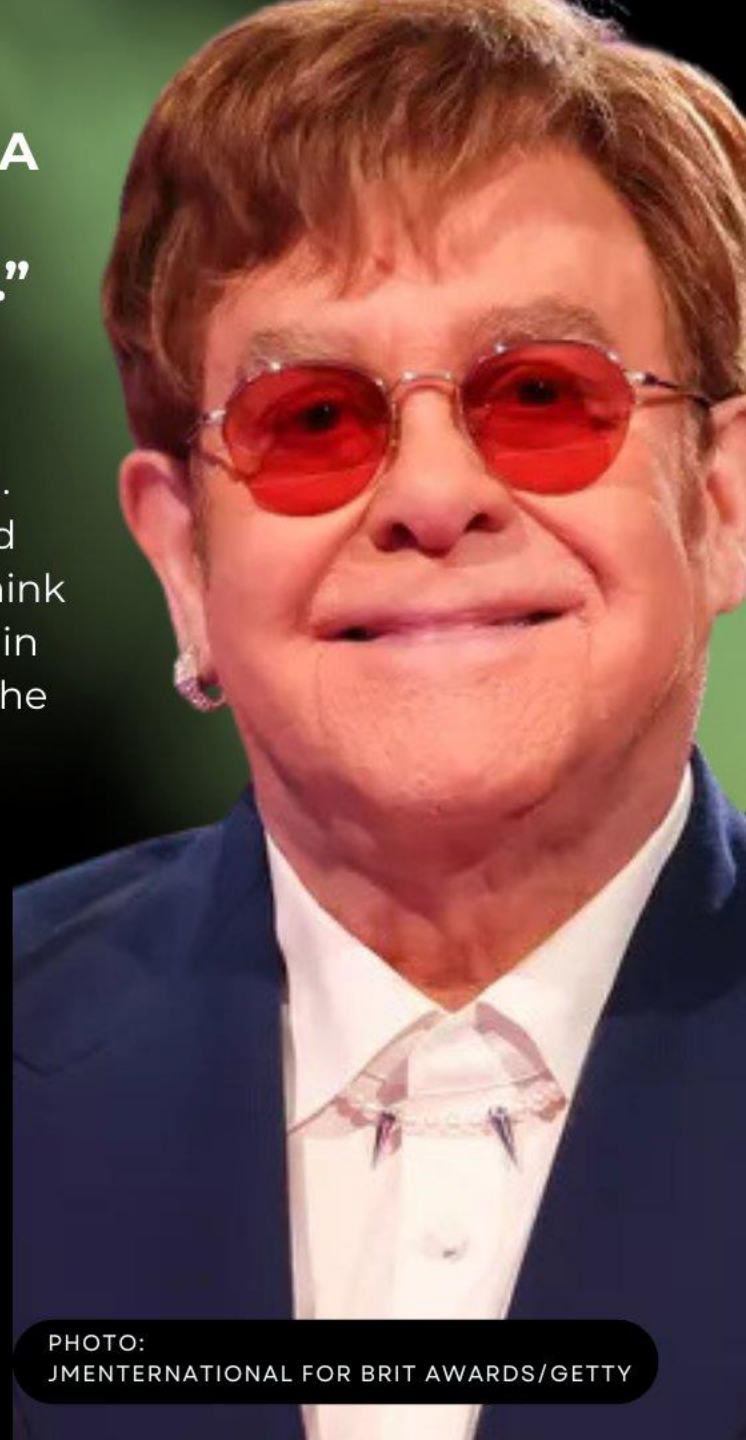


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Therapeutic Effects of Cannabis

Evidence Rating	Medical Disorders	Psychiatric Disorders
Rating 3: Strong Evidence	Spasticity in Multiple Sclerosis, Chronic Pain (Back and Neck), Neuropathic Pain	NONE
Rating 2: Equivocal Evidence	Chemotherapy-Induced Nausea/Vomiting HIV Wasting Syndrome	Major Depressive Disorder Panic Disorder Generalized Anxiety Disorder PTSD SUDs
Rating 1: Minimal Evidence	Glaucoma	NONE
CLEAR HARMS	--	Schizophrenia Bipolar Disorders

Hill, K.P. (2015) JAMA.313: 2474-2483; Halah, M.P. et al. (2016). Curr. Addict. Rep. 3: 450-462; George, T.P. et al., 2018. Can. J. Psychiatry. 63: 447-450.

Case Review




- Jessica is a 19 year old University of Toronto undergraduate student who was admitted to the Early Psychosis Unit at CAMH in an acutely psychotic and agitated state. She is in her sophomore year, and has become increasingly isolated and bizarre. She started smoking marijuana at age 17, and since entering college, her pot use has been daily.
 - In the past month, her roommate observed that she would lock herself in their room, and the room smelled of pot. She has become increasingly suspicious of the other students in her dorm, and she told her Residence Assistant that she felt the other students were stealing from her and trying to poison her. The Dean of Students called her parents (who were vacationing in Tuscany) and the police were called and she was brought to the CAMH Emergency Department.
 - She believes that her pot smoking is the “only thing keeping me sane”.
- 

TABLE. A comparison of the clinical features of idiopathic versus cannabis-induced psychosis

Primary psychosis (eg, schizophrenia)	Cannabis-induced psychosis
Cannabis urine toxicology sometimes positive	Positive cannabis urine toxicology
Variable reported cannabis use (25% prevalence of positive cannabis urine toxicology in schizophrenia)	Heavy cannabis use within past month
Symptoms appear before heavy substance use	Symptoms appear only during periods of heavy substance use/sudden increase in potency
Symptoms persist despite drug abstinence	Symptoms abate or are reduced with drug abstinence
Antipsychotics markedly improve symptoms	Antipsychotics may/may not improve symptoms
Most often presents with delusions, hallucinations, and thought disorder	Often associated with visual hallucinations and paranoid ideation (eg, features of an “organic” psychosis)
Less insight about psychotic state	More aware of symptoms/insight about disease
Disorganized thought form (eg, loose associations, tangential or circumstantial speech)	Thought form more organized and sequential

Cannabis and in Psychiatric Disorders

- **Cannabis is the most commonly used illicit drug in people with schizophrenia and mood and anxiety disorders:**
 - ~25% cannabis use disorder (CUD) in SZ (Koskinen et al., 2010) versus general population (~3%; Hasin et al., 2015)
 - ~35-45% CUD in Major Depression and Bipolar Disorder (Turna et al., 2017; Lucatch et al., 2018)
 - More common among male SMI patients (Koskinen et al., 2010)
- **Negative impact on course of the disorder** (Murray et al., 2017):
 - Longer psychotic and mood episodes
 - Role of THC versus Cannabidiol (CBD)
 - More relapses and re-hospitalizations
 - Increased treatment needs

Darby Lowe

MSc: 2018-2020

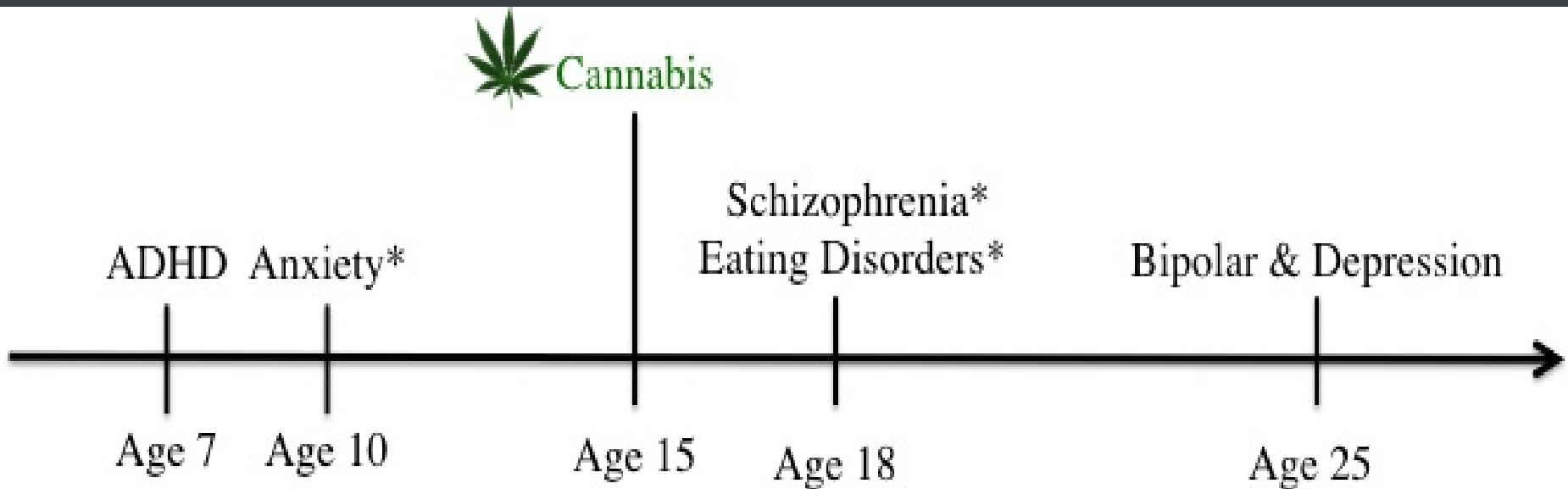
PhD UC Berkeley: 2024-



Murray, R.M. et al. (2017). *Neuropharmacol.* 124: 89-104;

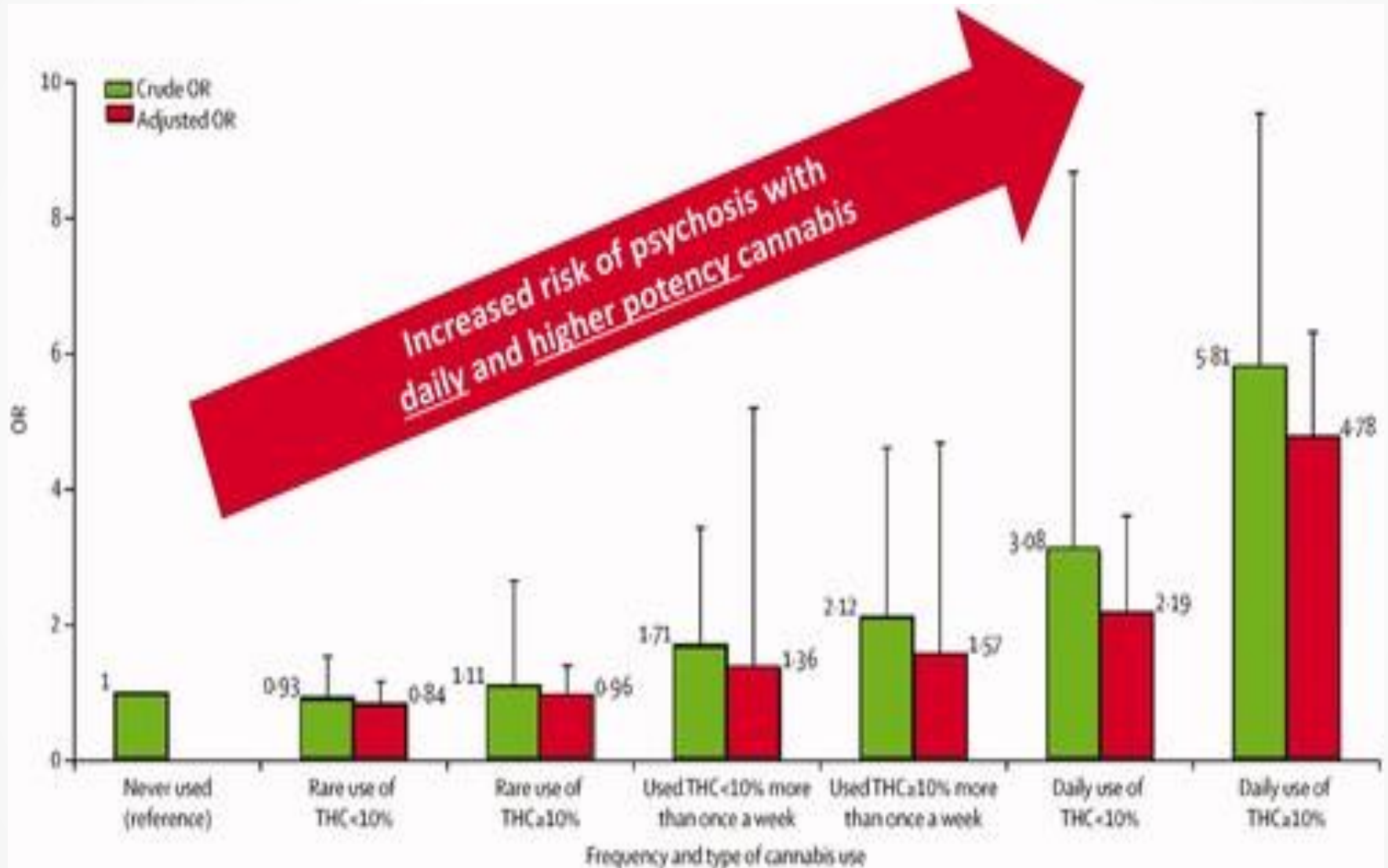
Lowe, D.J.E. et al. (2019). *Eur. Arch. Psychiat. Clin. Neurosci.* 269: 107-120.

Age of Onset: Cannabis and Mental Illness



Goodman, MS and George, TP (2015). From: Report on Cannabis and Youth, Canadian Centre on Substance Abuse (CCSA)

Cannabis and Psychosis: Relationship to Potency and Frequency of Use



Cannabis, COMT and Psychosis Risk

(Caspi et al., 2005. Biol. Psychiatry)

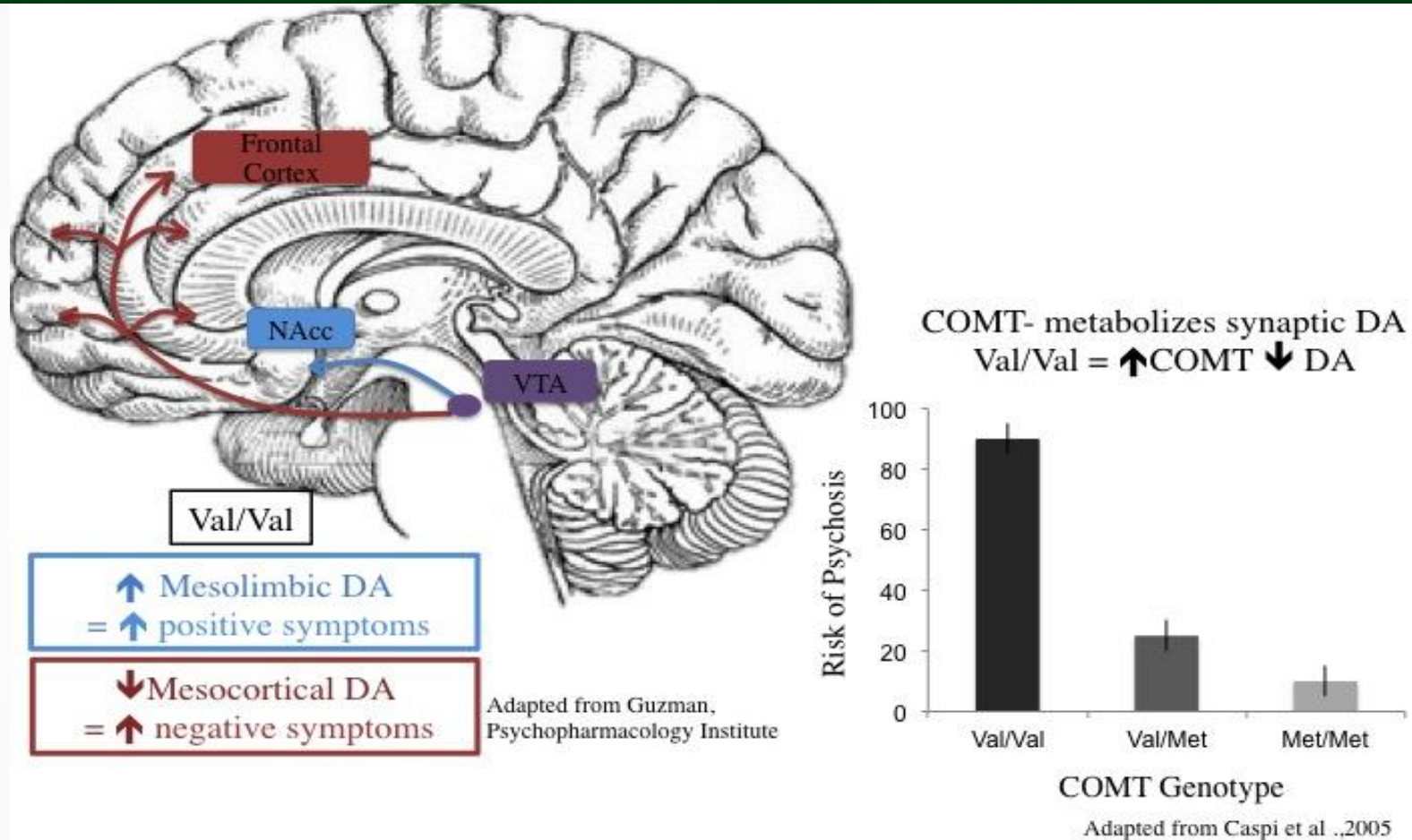


Figure 1 Legend. This figure depicts a potential explanation of how the valine (Val) allele of Catecholamine O-Methyltransferase (COMT), and its control over the enzymatic break down of synaptic dopamine (DA), may be implicated in the pathogenesis of schizophrenia.

What are the effects of sustained cannabis abstinence in people with schizophrenia?

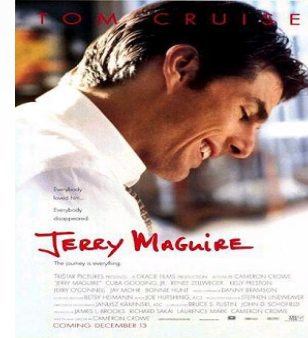


Rachel A. Rabin, Ph.D.

IMS Student: M.Sc. (2009-2011), Ph.D. (2012-2016)

**Associate Professor of Psychiatry,
McGill University**

Cannabis Abstinence Study Design



SCREEN

COGNITIVE
TRAINING
DAY

DAY 0

Clinical and
Substance Use
Assessments

Cognitive
Testing

Behavioral
Therapy

Urine Testing

DAY 7

Clinical and
Substance Use
Assessments

Behavioral
Therapy

Urine Testing

DAY 14

Clinical and
Substance Use
Assessments

Behavioral
Therapy

Urine Testing

DAY 21

Clinical and
Substance Use
Assessments

Behavioral
Therapy

Urine Testing

DAY 28

Clinical and
Substance Use
Assessments

Cognitive
Testing

Behavioral
Therapy

Urine Testing

\$300
ABSTINENCE
BONUS

FOLLOW
UP

Clinical and
Substance Use
Assessments

Cognitive Testing

Cannabis
Abstinence
Begins 12
Hours prior
to Day 0

Cognitive Battery

Attention
Verbal Learning and Memory
Working Memory
Visuospatial Working Memory
Motor Function
Impulsivity and Decision-Making
Processing Speed
Executive Function

Clinical Measures

PANSS- psychotic symptoms (SCZ))
CDSS- depression (SCZ)
HAM-D- depression
Marijuana Withdrawal Checklist
Marijuana Craving Questionnaire



Cannabis Abstinence Rates at Day 28

Total N=39	Abstainers	Non- Abstainers	Abstinence Rate
SZ (n=19)	8/19	11/19	42.1%
CTL (n=20)	11/20	9/19	55.0%

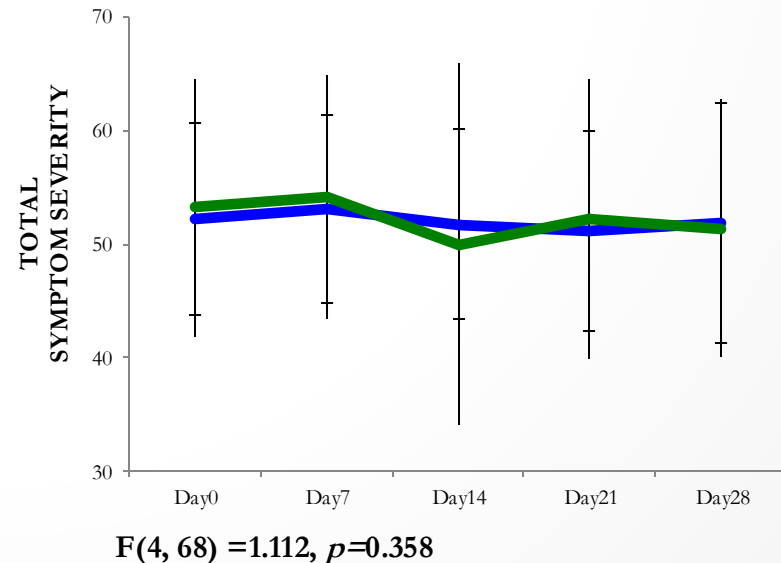
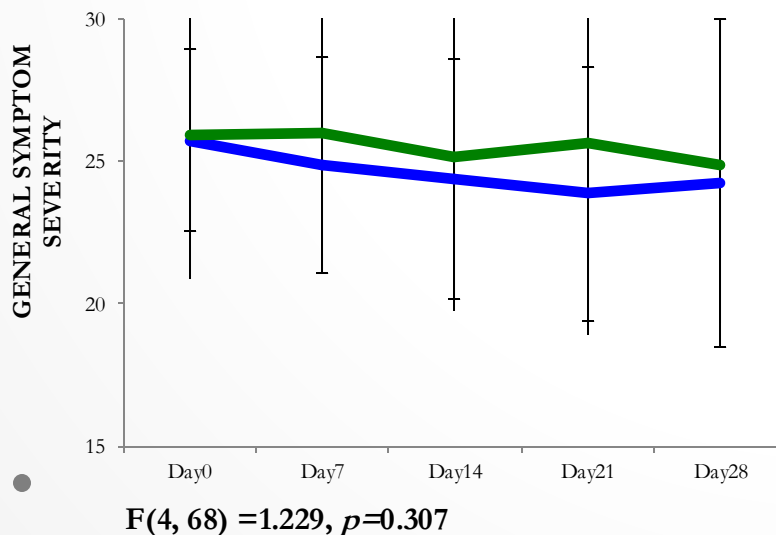
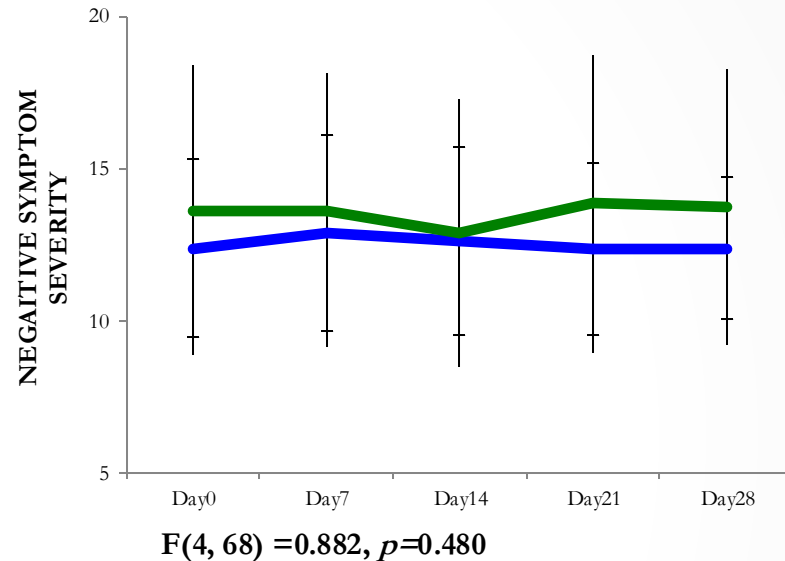
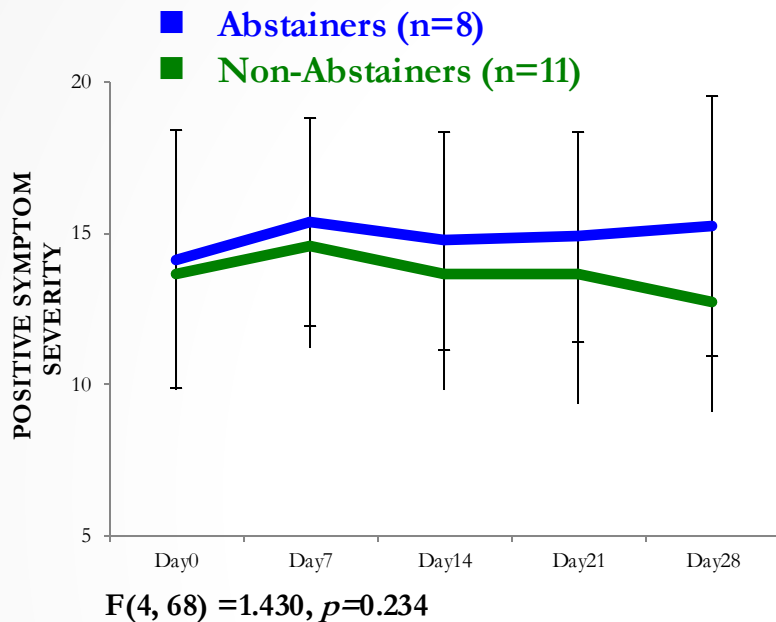
There was no statistical difference in rates of abstinence between patients and controls

$$\chi^2=0.648 \text{ (df=1), } p=0.527$$

- Rabin, R.A. et al. (2018). Schizophr. Res. 194: 47-54.

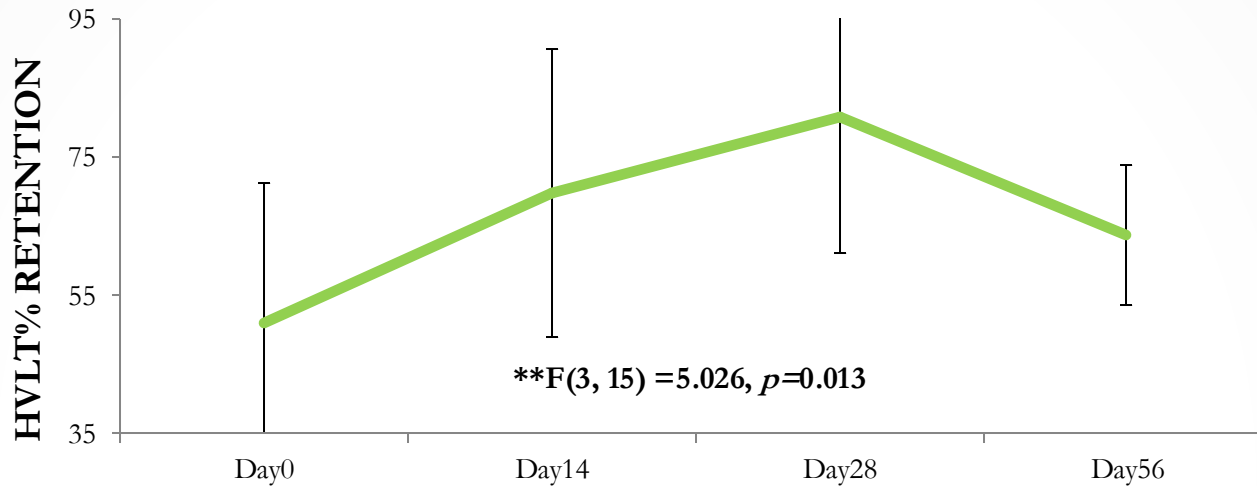
Psychotic Symptoms

Rabin, RA et al. (2018). Schizophr. Res. 194: 55-61.

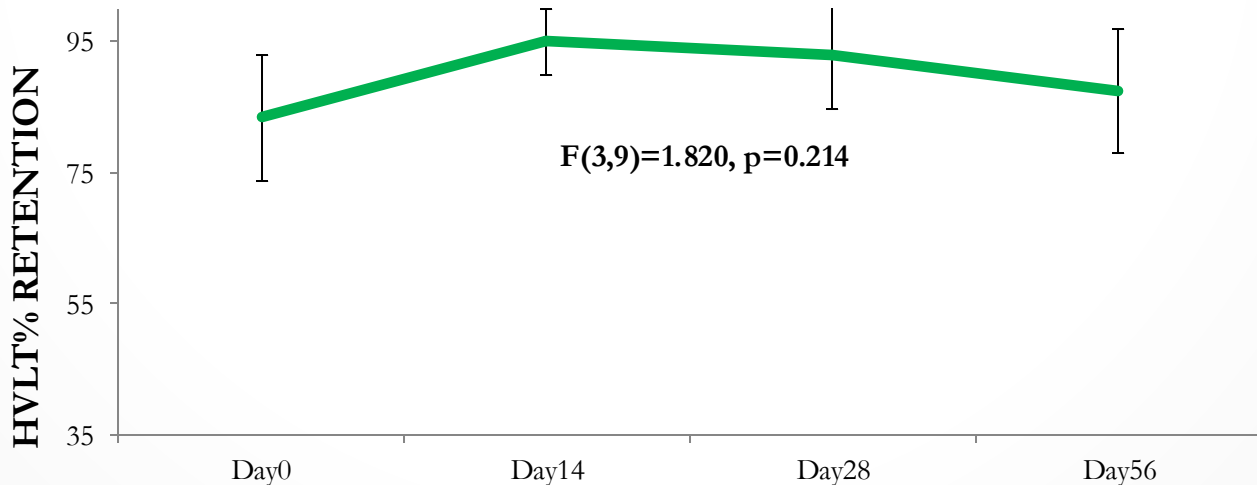


Verbal Learning and Memory

SCZ: N=6



CTRL: N=4



Cannabis Use in Major Depressive Disorder (MDD)

- Cannabis use and cannabis use disorder (CUD) are higher in those with MDD than those without.
- From 2006 to 2016, cannabis use among those with depression increased:
 - **Any use:** odds rose from **46% to 130%** higher than non-depressed peers.
 - **Daily use:** odds rose from **37% to 216%** higher than non-depressed peers.

Table 3. Change in the Prevalence of Past-Month Cannabis Use by Depression Status and Association Between Depression and Past-Month Cannabis Use Among US Adults Aged 20 to 59 Years, National Health and Nutrition Examination Survey 2005-2006 to 2015-2016

Past month cannabis use	Prevalence, weighted % (SE) ^a						Association between past-month cannabis use and depression, OR (95% CI)	
	2005-2006	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	Crude	Adjusted ^b
Any								
No probable depression	11.90 (1.18)	11.32 (0.60)	12.99 (0.96)	13.36 (0.94)	13.79 (0.71)	16.09 (1.90)	1 [Reference]	1 [Reference]
Probable depression	17.81 (3.77)	17.68 (2.19)	21.51 (3.31)	24.36 (4.58)	26.09 (3.53)	31.88 (2.89)	2.03 (1.74-2.36)	1.90 (1.62-2.24)
Daily or near-daily								
No probable depression	3.59 (0.57)	3.22 (0.45)	4.74 (0.55)	3.88 (0.49)	4.95 (0.43)	5.27 (0.92)	1 [Reference]	1 [Reference]
Probable depression	7.03 (2.84)	4.00 (1.26)	7.78 (1.49)	11.05 (3.17)	11.47 (2.13)	15.59 (3.19)	2.39 (1.88-3.04)	2.29 (1.80-2.92)

Abbreviation: OR, odds ratio.

^a Total number of participants was 16 216.

^b Control covariates included gender, age, race, education, marital status, annual family income, and past-year alcohol, cocaine, heroin, and methamphetamine use.

Gorfinkel et al.
2020 JAMA
Netw. Open

Cannabis & Mood Disorders

Clinical domain	Number of studies supporting an adverse effect of cannabis	Number of studies supporting no effect of cannabis	Number of studies supporting a therapeutic effect of cannabis	General findings
MDD Symptom or Diagnosis Development	29	11	0	Cannabis use may be moderately associated with elevated depressive symptoms or increased risk of developing MDD (72.5% of studies).
BD Symptom or Diagnosis Development	9	3	0	Cannabis use may be moderately associated with elevated manic symptoms or increased risk of developing BD (75% of studies)
Prognosis of MDD	10	1	0	Cannabis use does not appear to improve MDD-related outcomes and is associated with poorer treatment outcomes in MDD (90.9% of studies)
Prognosis of BD	15	3	1	Cannabis use is associated with poorer treatment outcomes in BD (78.9% of studies).

Cannabis Abstinence and Major Depression

MS

Figure 2 Trajectory of HDRS-17 Depression Severity (n=11)

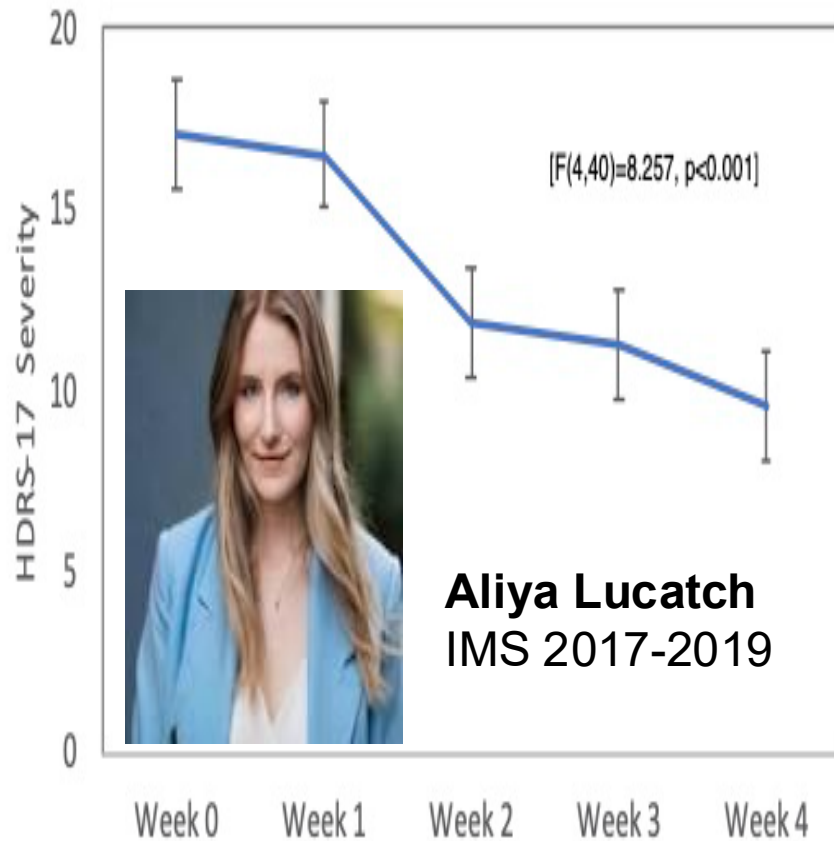
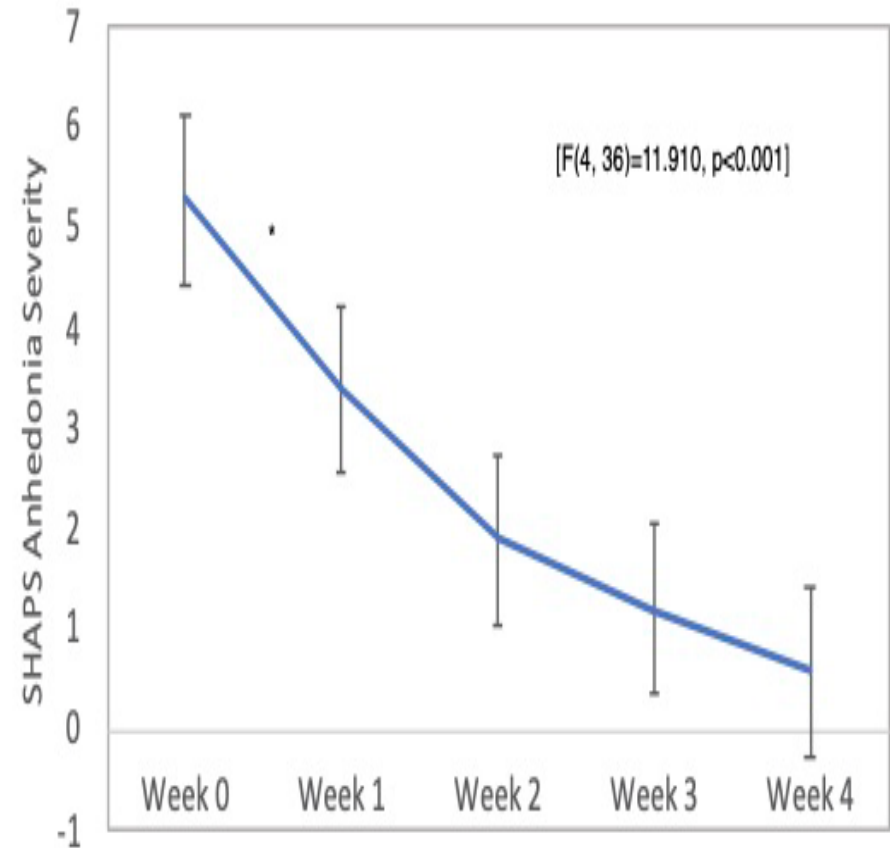
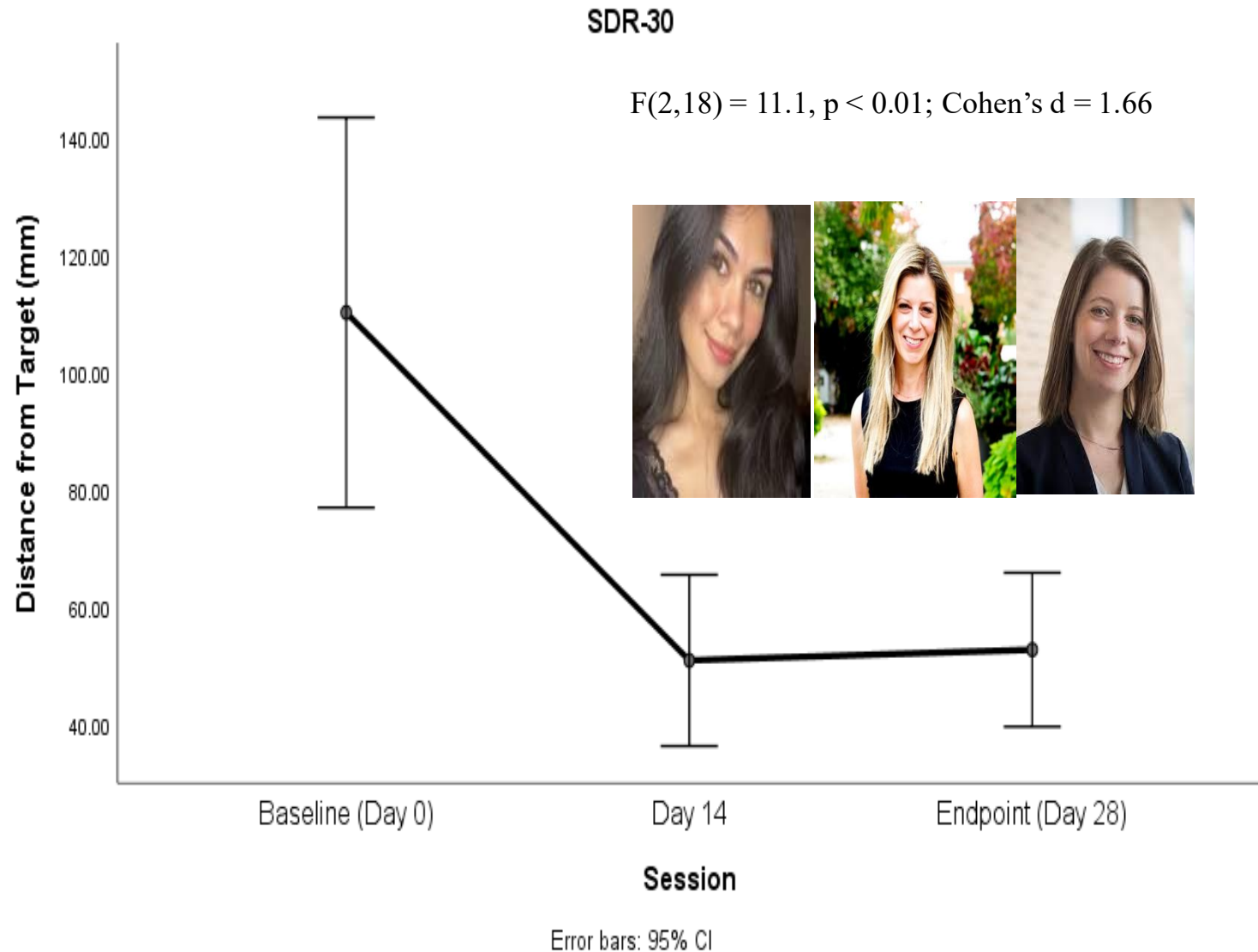


Figure 3 Trajectory of SHAPS Anhedonia Severity (n=10)



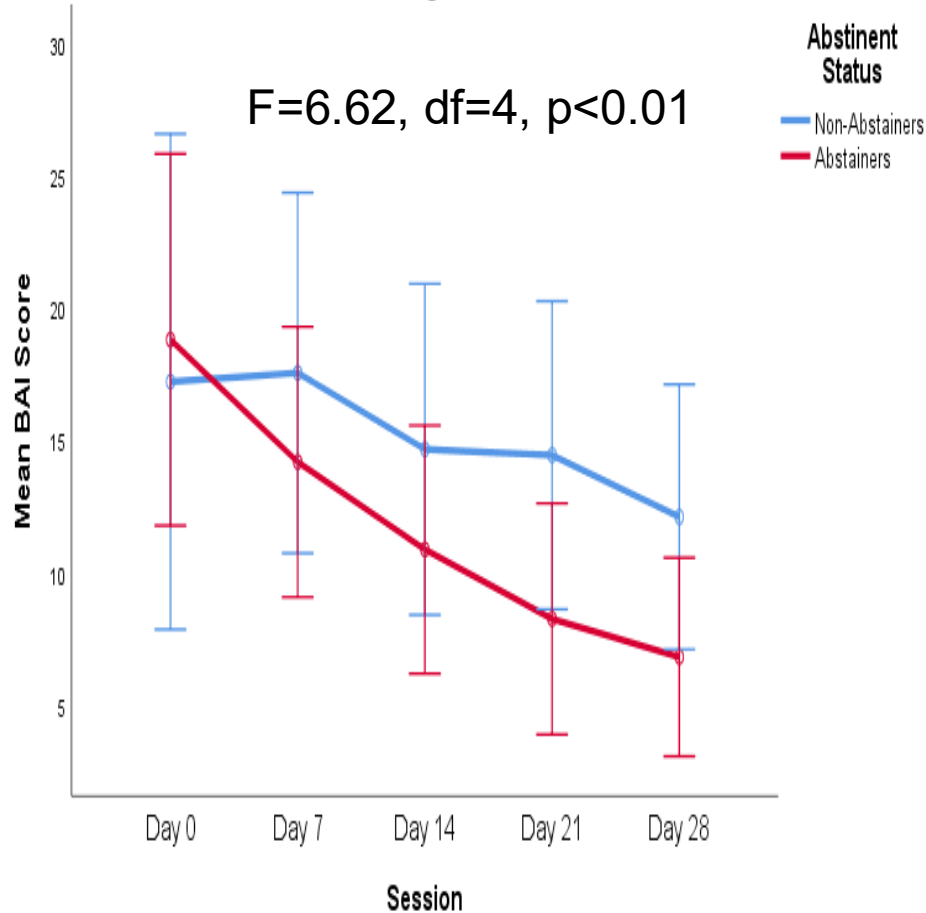
Lucatch, A.M. et al. (2020). Can. J. Addict. 11: 33-41.

Cannabis Abstinence and Visuospacial Working Memory (VSWM; SDR 30 Sec Delay) in Major Depression

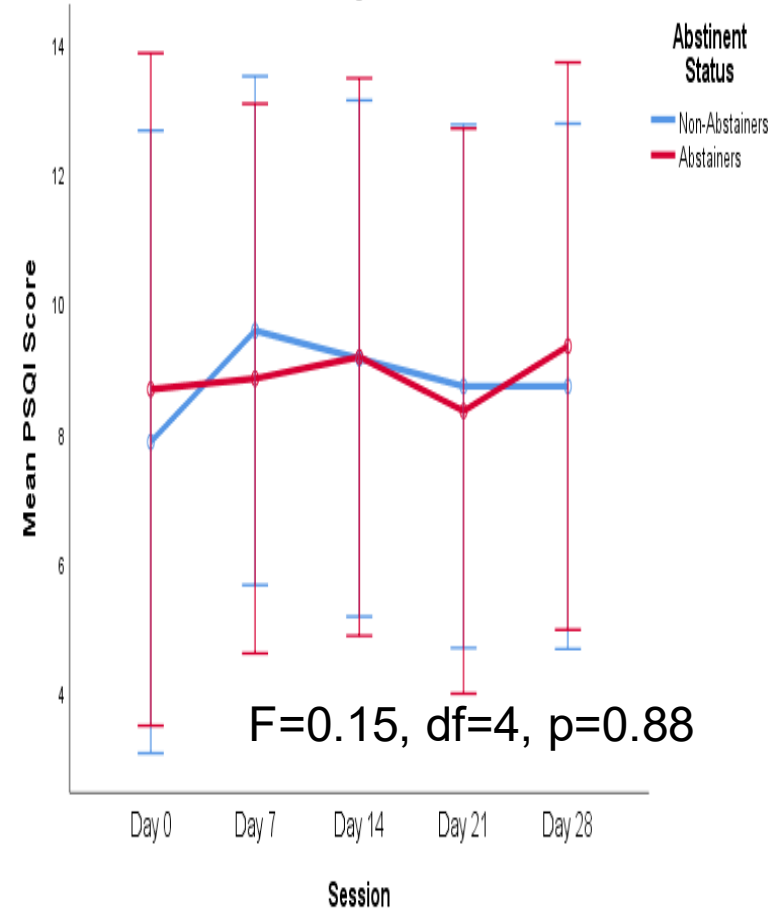


Effects of Extended Cannabis Abstinence on Anxiety and Sleep

Changes in Global BAI Scores



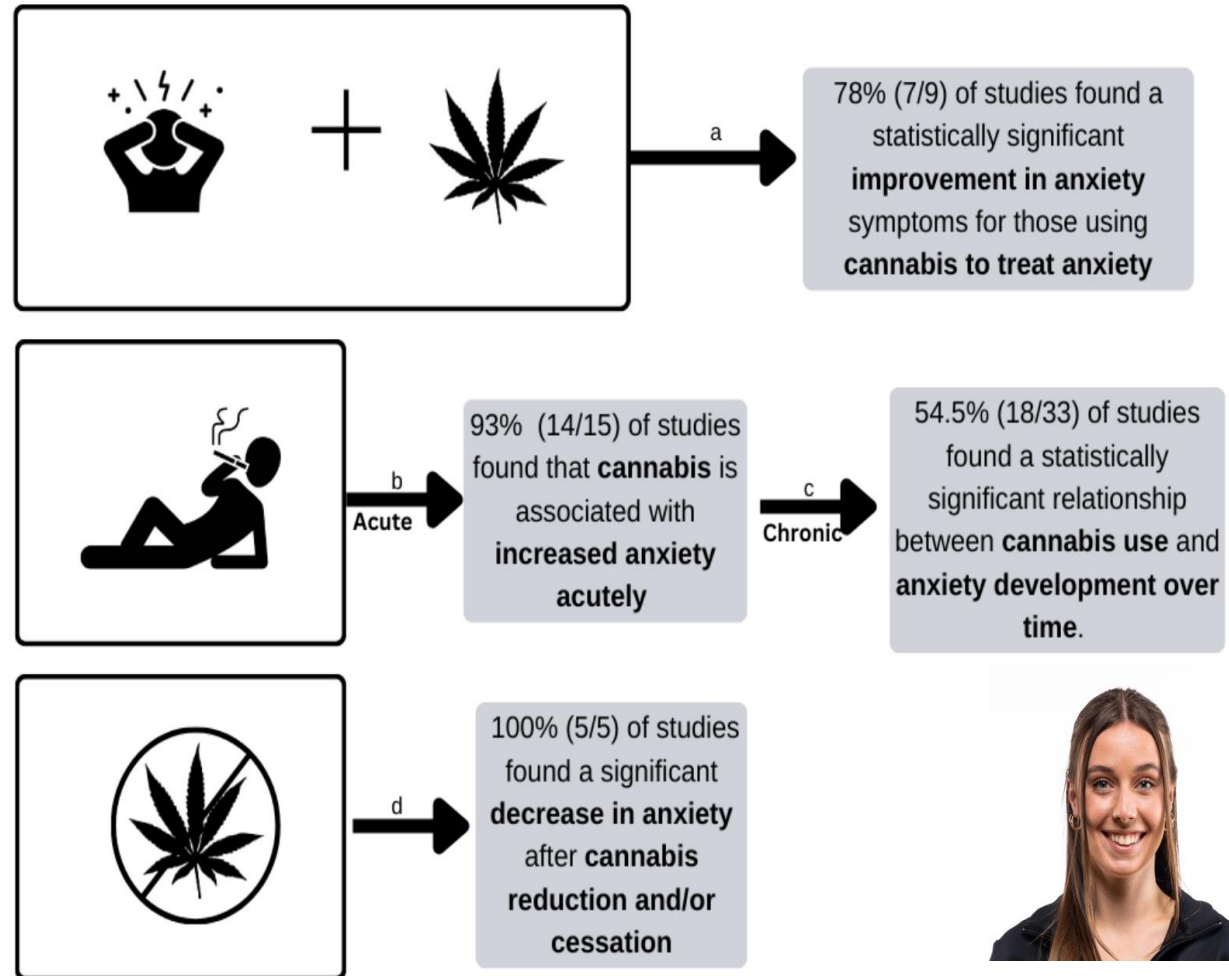
Changes in Global PSQI Scores



The Complex Relationship Between Cannabis and Anxiety

Cannabis and Anxiety

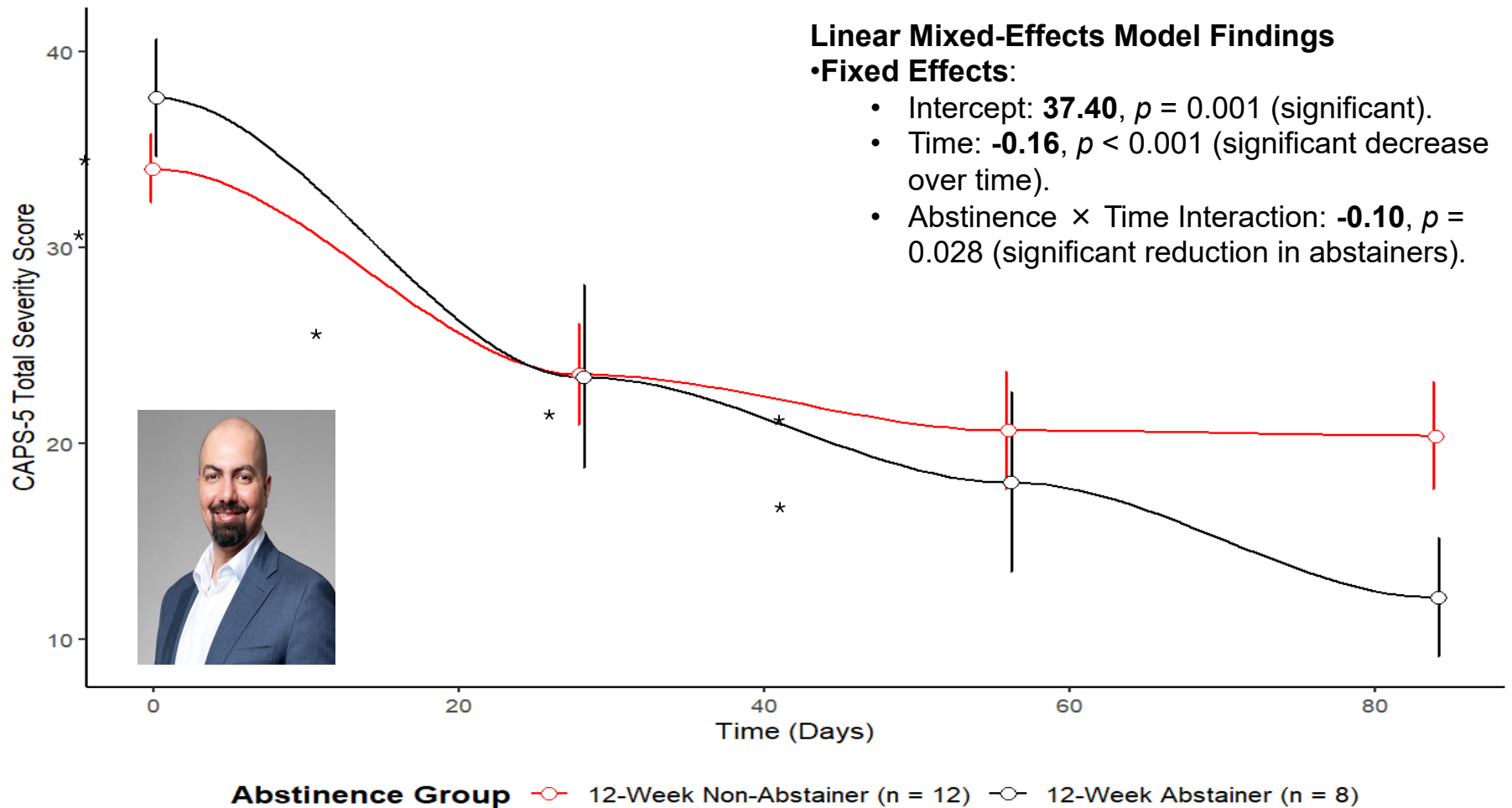
The complicated relationship



*Blyth, L.G. et al. (2025).
Curr. Addict. Rep. 12: 35*

Cannabis Abstinence and PTSD Symptoms

CAPS-5 Total Severity Score Over Time by 12-Week Abstinence Status



Treatment of Cannabis Use Disorder

- **Behavioral:**
 - Motivational interviewing (MI)
 - Cognitive-Behavioural therapy (CBT)
 - Contingency management (CM)
- **Medications:** *None are FDA approved*
 - Agonist Substitution – Sativex (THC/CBD, 1:1, e.g. Allsop et al., 2016; Trigo et al., 2018), Marinol (Dronabinol), Cesamet (Nabilone) - ??
Antagonists (e.g. rimonabant)
 - N-Acetylcysteine (NAC) – Gray et al (2012). Am. J. Psychiatry.
 - Antidepressants (bupropion, nefazadone)/Mood Stabilizers (valproate)
 - FAAH Inhibitors (D'Souza et al., 2019. Lancet Psychiatry)
 - Signaling Specific CB1R Inhibition (AEF0117; Haney et al., 2023. Nat. Med.)

**ARTICLE** **OPEN**

A systematic review and meta-analysis of neuromodulation therapies for substance use disorders

Dhvani D. Mehta^{1,2}✉, Angela Praecht^{1,2}, Heather B. Ward^{ID}³, Marcos Sanches¹, Maryam Sorkhou^{ID}^{1,2}, Victor M. Tang^{ID}^{1,2}, Vaughn R. Steele^{ID}⁴, Colleen A. Hanlon^{ID}⁵ and Tony P. George^{ID}^{1,2}✉

Substance Use Disorder	rTMS [Total N = 2406; 51 Studies]		tDCS [Total N = 1582; 36 Studies]		DBS [Total N = 48; 7 Studies]	
	Population	Studies with Positive Outcomes (Effect Size – Active vs. Control)	Population	Studies with Positive Outcomes (Effect Size – Active vs. Control)	Population	Studies with Positive Outcome (Effect Size – Post vs. Pre.)
Alcohol [N=1369; 34 Studies]	n = 607 (16 Studies)	7/16 (44%) Hedge's $g = -1.01$, 95% CI [-1.62, -0.40]	n = 734 (14 Studies)	9/14 (64%) Hedge's $g = -0.31$, 95% CI [-0.62, 0.002]	n = 28 (4 Studies)	4/4 (100%) Hedge's $g = -2.36$, 95% CI [-3.31, -1.41]
Tobacco [N=1239; 28 Studies]	n = 781 (16 Studies)	14/16 (88%) Hedge's $g = -1.36$, 95% CI [-2.09, -0.63]	n = 448 (11 Studies)	7/11 (64%) Hedge's $g = -0.50$, 95% CI [-0.87, -0.13]	n = 10 (1 Study)	1/1 (100%) Hedge's $g = -0.40$, 95% CI [-1.28, -0.49]
Cannabis [N=33; 2 Studies]	n = 33 (2 Studies)	1/2 (50%) Hedge's $g = 0.04$, 95% CI [-0.49, 0.57]	n = 0 (0 Studies)	NA	n = 0 (0 Studies)	NA
Cocaine [N=321; 9 Studies]	n = 227 (6 Studies)	3/6 (50%) Hedge's $g = -0.73$, 95% CI [-1.57, 0.11]	n = 94 (3 Studies)	1/3 (33%) Hedge's $g = -0.19$, 95% CI [-0.27, -0.11]	n = 0 (0 Studies)	NA
Methamphetamine						

Repetitive Transcranial Magnetic Stimulation (rTMS)

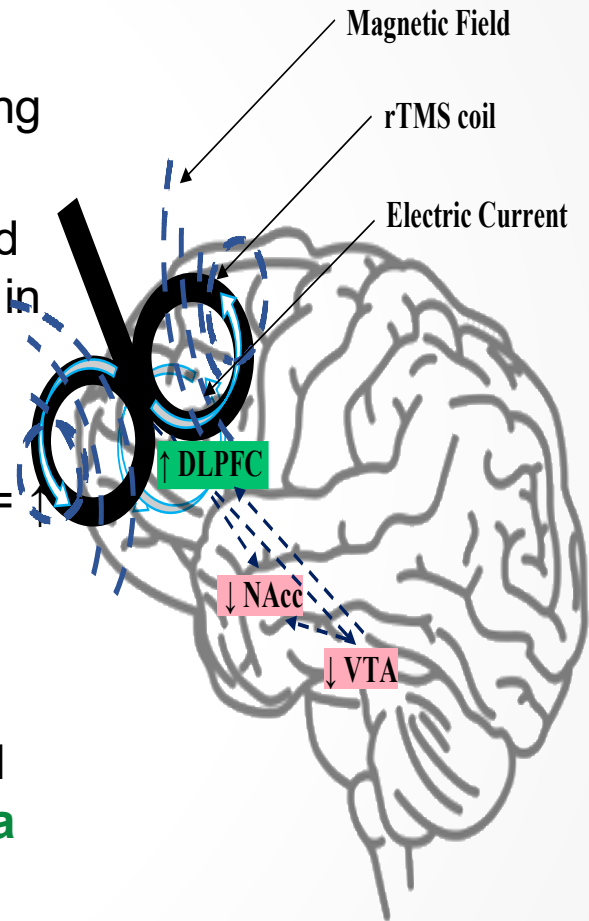
- rTMS uses weak magnetic pulses to alter neuronal firing of inhibitory/excitatory pathways in the brain.
- Both low and high frequency rTMS procedures directed to DLPFC have shown therapeutic promise/tolerability in preliminary studies:

- **Schizophrenia**

- rTMS enhances hypoactive DLPFC function = ↑ cognitive control (**Barr et al., 2013**)

- **Substance Use Disorders (e.g., CUD)**

- rTMS to DLPFC normalizes hyperactive subcortical regions (NAcc, VTA) = normalized reward processing (**Coles et al., 2018; Mehta et al., 2024**)



Objective: CANSTIMulate Study

To determine the effects of 4-weeks of active (20-Hz) vs. sham rTMS treatment directed bilaterally to the DLPFC on cannabis use outcomes in outpatients with comorbid schizophrenia and CUD.





Karolina Kozak, Ph.D.



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Julia Sasiadek, M.Sc.

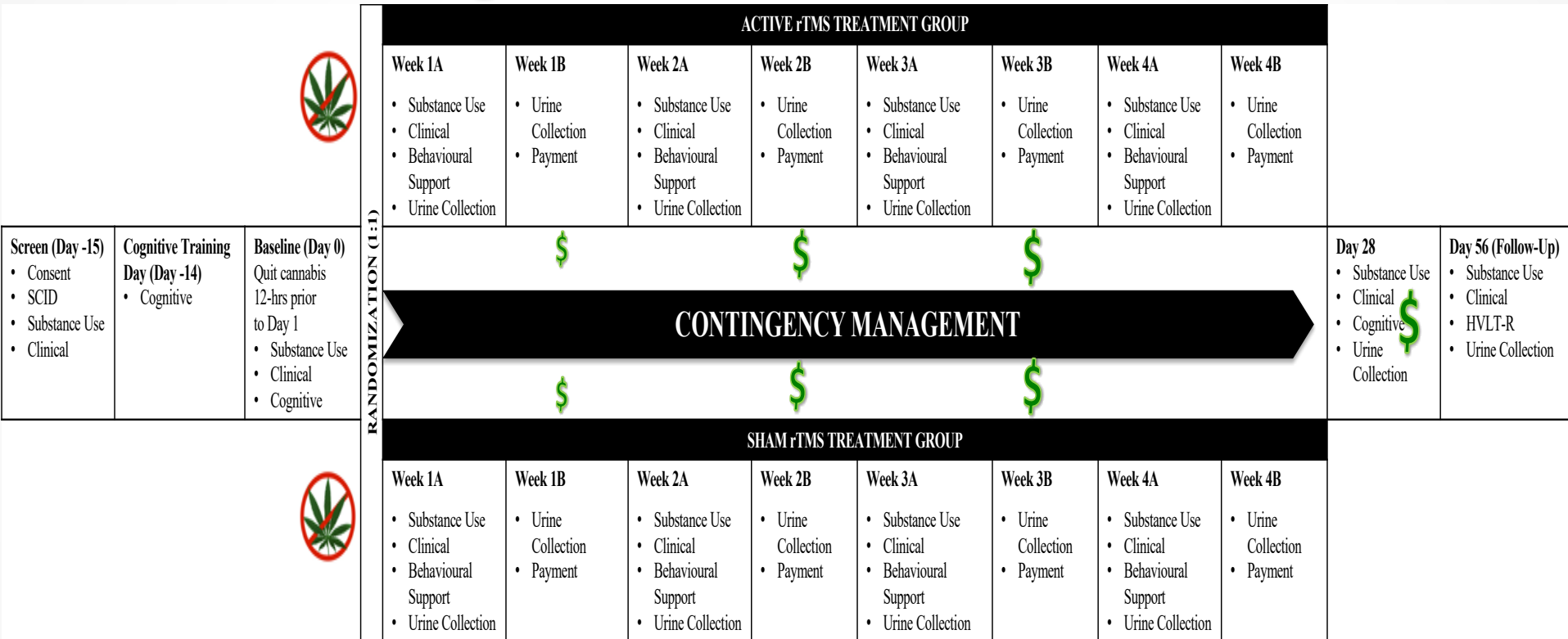
Inclusion Criteria

1. Male; Female;
2. Age 18-55;
3. Meet DSM-5 criteria for schizophrenia and cannabis use disorder (cannabis use ≥ 1 g/day; CUDIT score ≥ 12);
4. Urinary baseline THC positive;
5. Full scale IQ ≥ 80 ;
6. Non-smokers OR cigarette smoker;
7. Treatment-seeking for CUD (MCL ≥ 7 ; intention to quit < 30 days).

Exclusion Criteria

1. DSM-5 diagnoses of alcohol or substance use disorder in the past 6 months (other than cannabis, caffeine or nicotine);
2. Head injury resulting in loss of consciousness > 5 minutes or hospitalization;
3. Major neurological or medical illness including seizure disorder of first-degree relative with history of seizures;
4. Metallic implants;
5. History of rTMS treatment;
6. Pregnancy.

Randomized, Double-Blind, Sham-Controlled Trial in SZ Outpatients with Comorbid CUD



Substance Use Assessments

- MCQ-SV
- MWC
- TLFB
- CO

Clinical Assessments

- PANSS
- CDSS
- SAFTEE

Cognitive Assessments

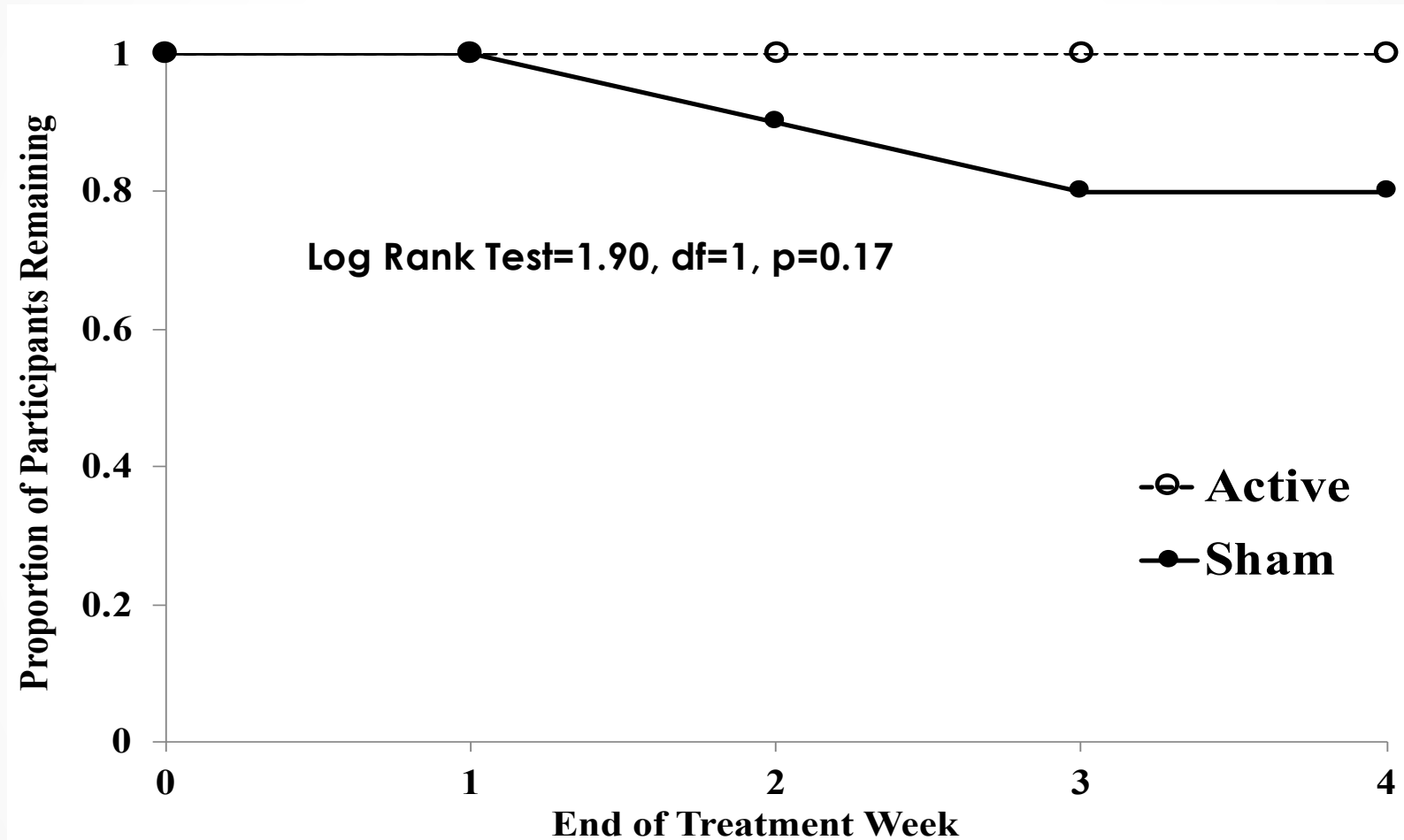
- Impulsivity (BART, KDDT)
- Verbal memory, learning, retrieval and recognition (HVLT-R)
- Working memory (SDR, Digit Span Backward)
- Attention (CPT, TMTA, Digit Span Forward/Total)
- Executive Function (TMTB, TOL, WCST)
- Motor Function (Grooved Pegboard)
- Sensory Memory and Undirected Attention (MMN)

Urine Collection

- Narcocheck
- THC-COOH Toxicology

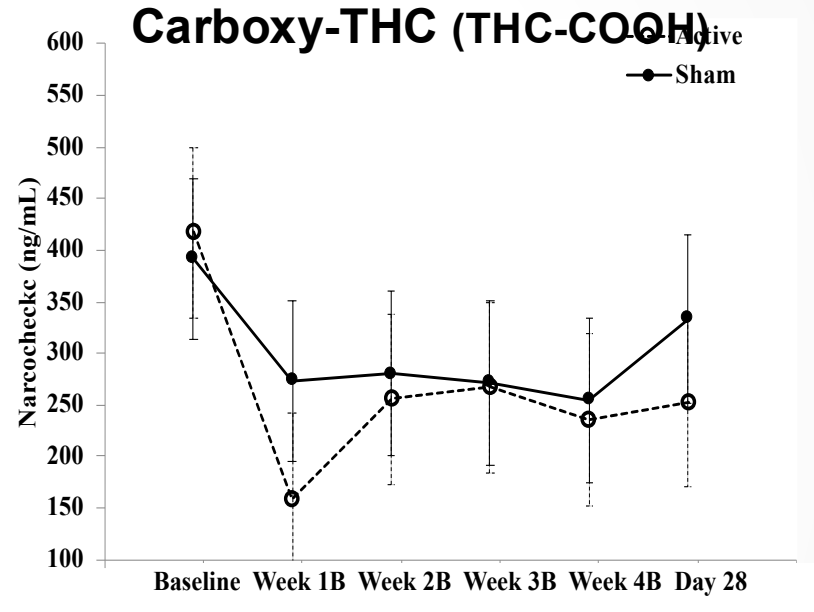
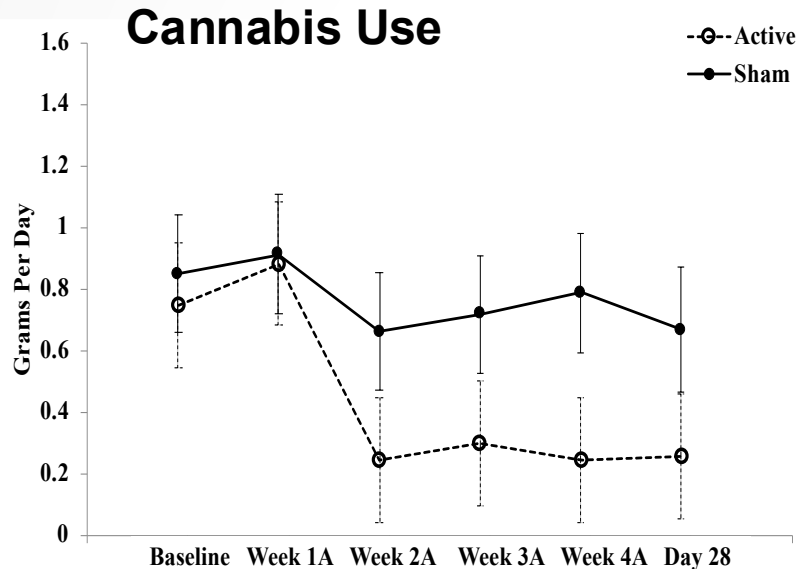


Treatment Retention in Active and Sham rTMS Groups



Kozak, K., Lowe, D.J.E. et al. (2022). Schizophrenia. 8:2

Change in Cannabis Use in Active versus Sham rTMS Groups

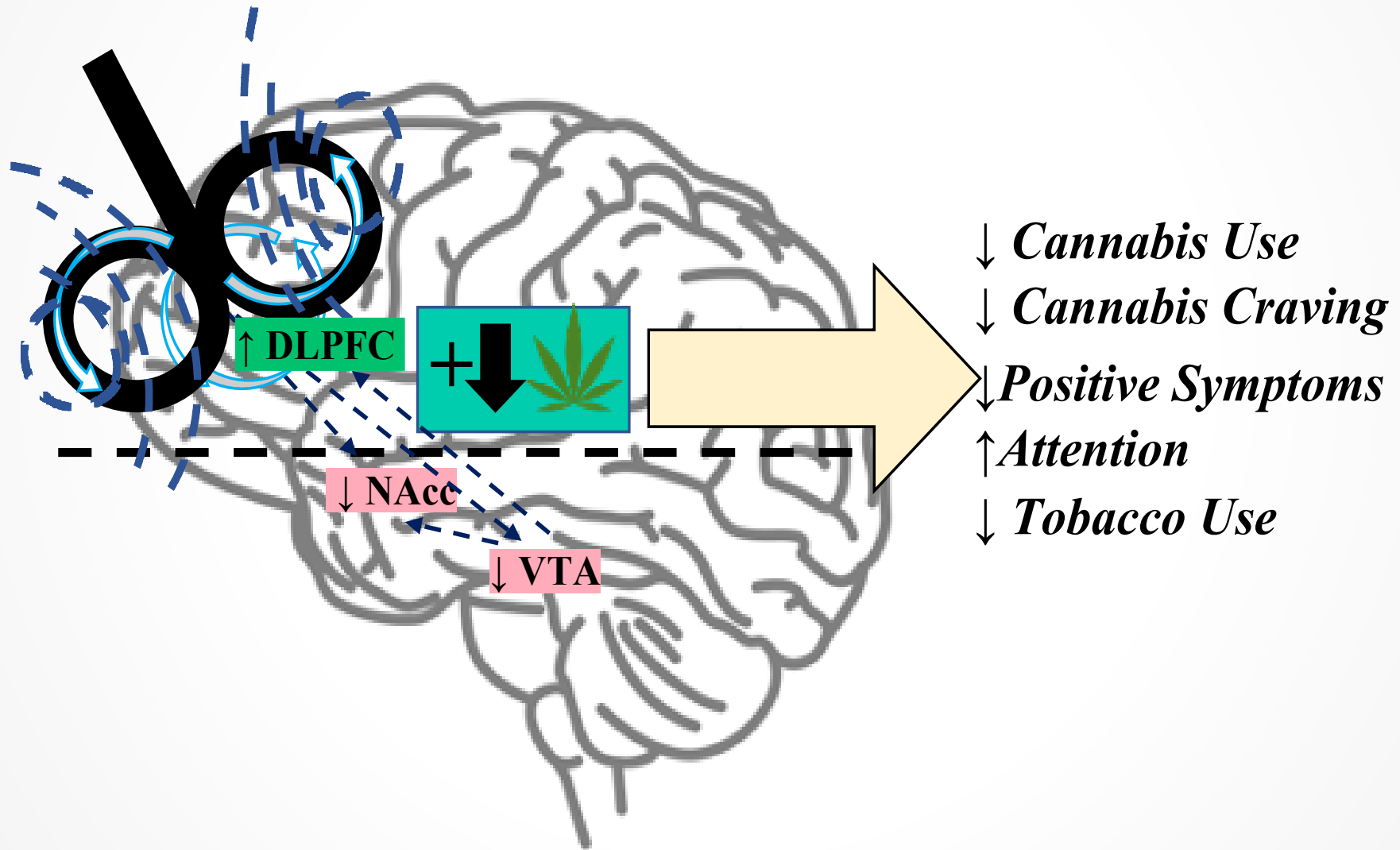


Key Takeaway: ↓ in cannabis use observed over time, with greater reductions in the active versus sham rTMS group.

*Kozak-Bidzinski, K., Lowe, D.J.E. et al. (2022).
Schizophrenia. 8:2.*



Proposed Mechanism of Action of rTMS for Treating Schizophrenia and CUD



CONCLUSIONS

- Cannabis use disorder is common in people with psychiatric disorders, and should be of clinical concern to psychiatrists.
- Novel treatment approaches based on a biopsychosocial understand of potential mechanisms relevant to cannabis and mental illness are needed. CM and brain stimulation may be two such approaches.



Thank you!



Funding Support:



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