

# Cannabis in the Legalization Era: Caveat “H-Emptor”

City-Wide Medical Grand Rounds,  
Department of Medicine, University of Toronto  
Toronto, ON, January 16, 2019

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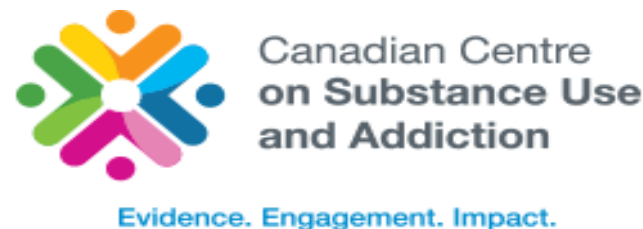
**camh** Centre for Addiction  
and Mental Health



Psychiatry  
UNIVERSITY OF TORONTO

# Disclosures - Tony P. George

- Funding from NIH/NIDA, CIHR, CFI
- Member, Addiction Risks and Mechanisms (ARM) IRG, NIH
- Member, Scientific Advisory Council, CCSUA
- Deputy Editor, *Neuropsychopharmacology*
- Advisory Boards, Drug-Free Kids (DFK) and Families for Addiction Recovery (FAR)



# Objectives

1. To understand the biological effects of cannabis.
2. To appreciate the implications of Canada's new cannabis legalization framework for the general population, and in vulnerable populations such as youth and people with mental illness.
3. To appreciate treatment approaches for problematic cannabis use.

Today's cartoon, by Kim Warp:

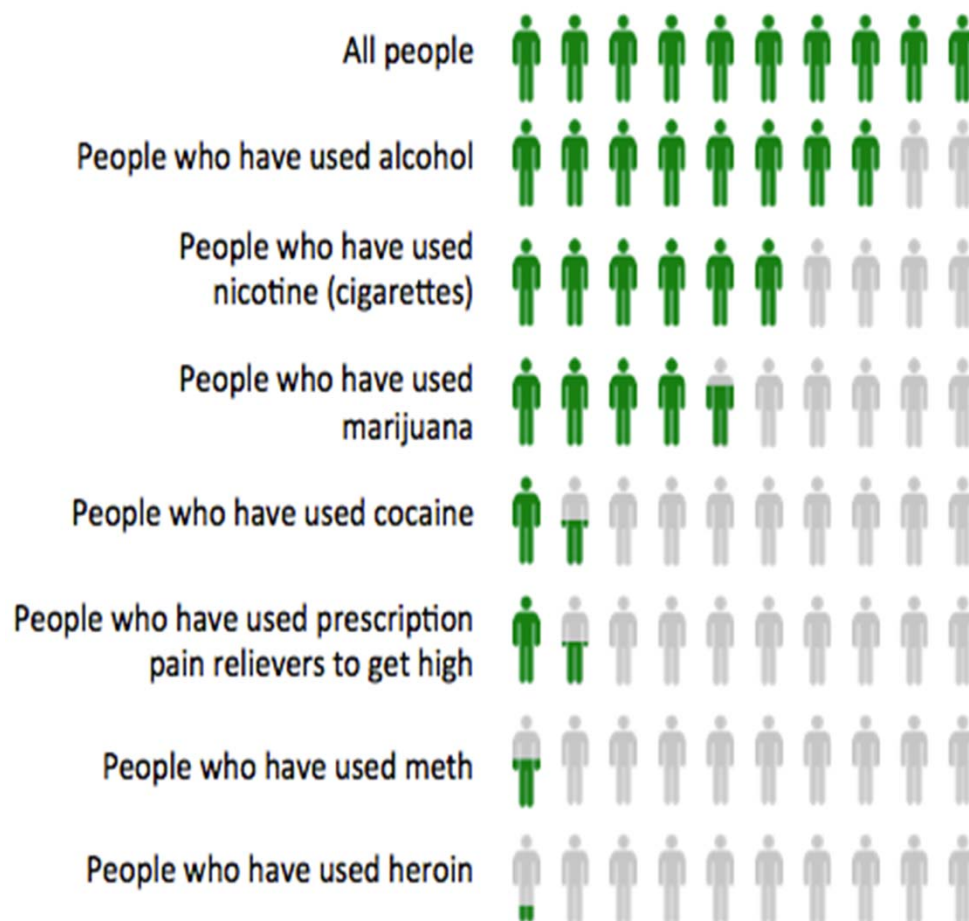


*“You’re totally paranoid—no one is swarming the border.”*

# Cannabis

- 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%)
- Lifetime use prevalence ~45%
- Derived from *Cannabis Sativa* plant

FIGURE 1. Lifetime use of mood-altering drugs



Hill, K.P (2015). *Marijuana: The Unbiased Truth About the World's Most Popular Drug*, Hazelton Press.

# Cannabis – Focus on THC

Contains over 400 compounds; 60 cannabinoids

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

THC is a partial agonist

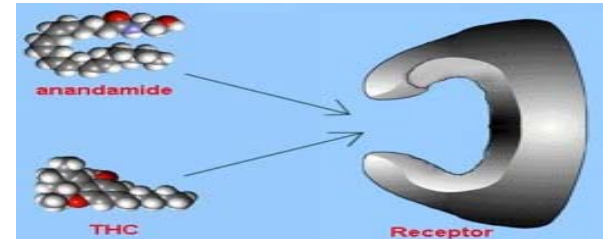
- Acts at cannabinoid 1 receptors (CB1R)
- High density in cerebellum, hippocampus - responsible for psychomotor and memory impairment
- Endogenous ligand: **anandamide**

Highly lipophilic: Fat-soluble

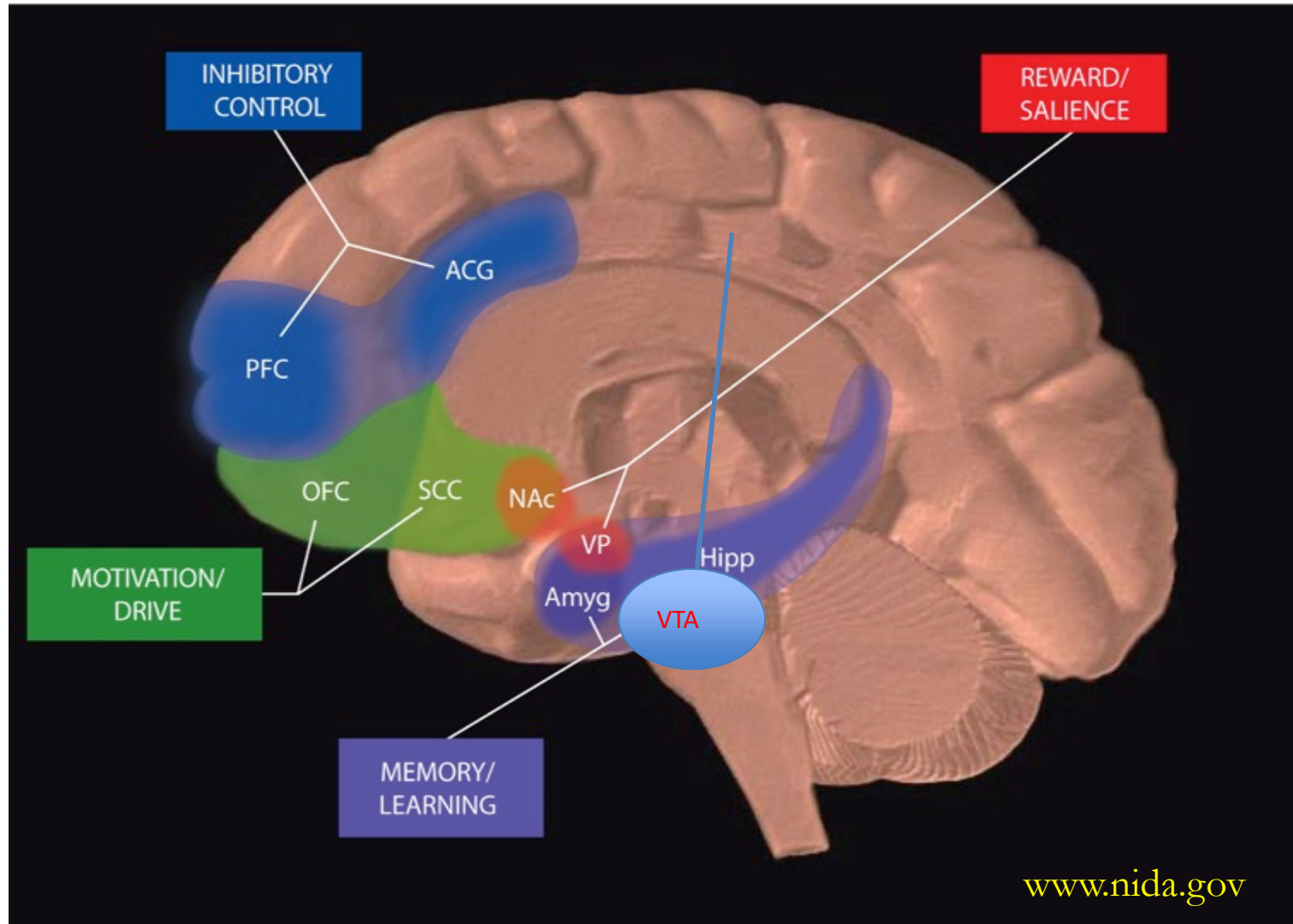
- Long half-life
- Deposits in adipose tissue and re-released into blood
- Recurrent use can lead to cannabinoid accumulation (Ashton 1999)

Metabolized into 11-OH-THC and THC-COOH

- Complete elimination may take up to one-month (Maykut, 1985)



# Neurocircuitry of Substance Use Disorders



# Cannabidiol (CBD)

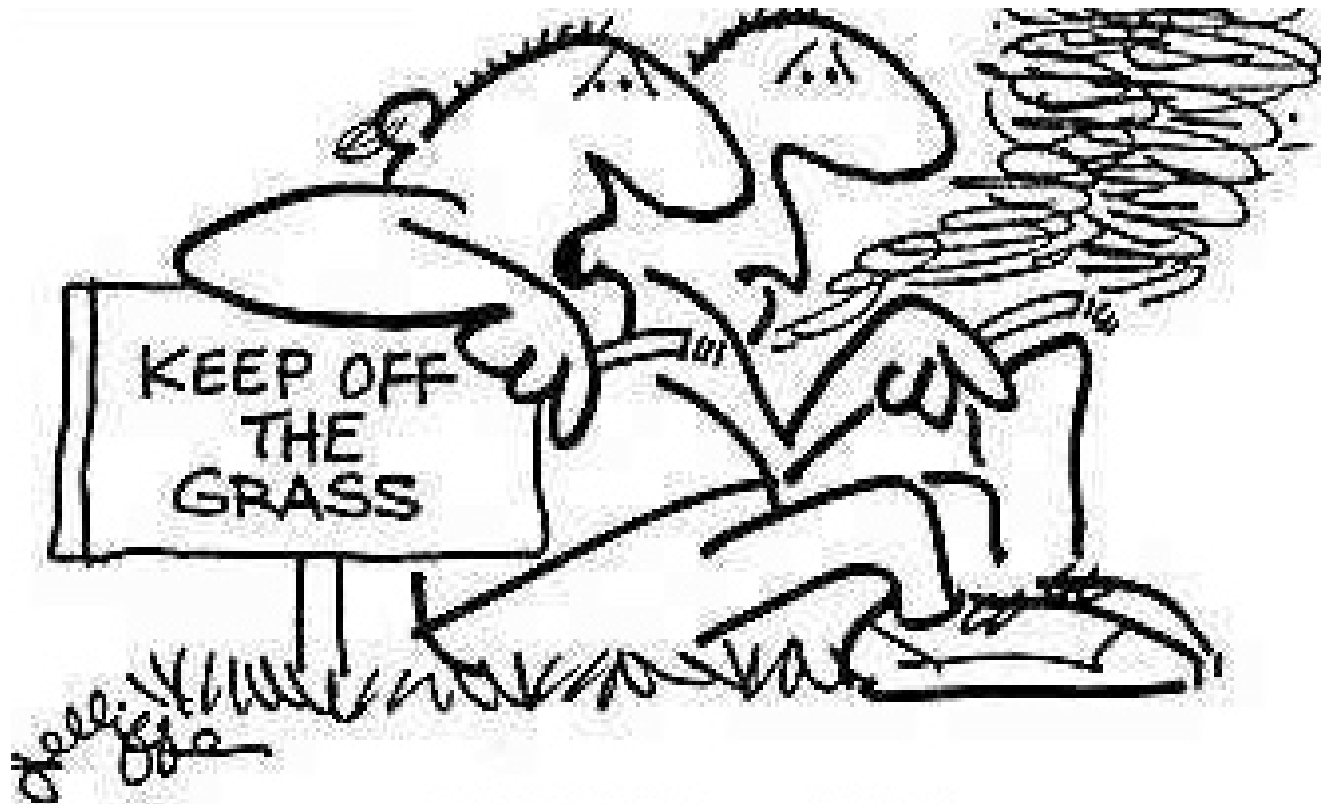
- Another component of cannabis, % content varies by strain
- Opposes actions of THC, acts on CB1 and CB2 receptor sites
- Relevance to psychiatry: evidence for antipsychotic, anti-anxiety, antidepressant, pro-cognitive and anti-craving effects
- Recently approved for various forms of pediatric epilepsy (e.g. Dravet's Syndrome) in the USA (Epidolex).



# Clinical Features

- There is a clear dependence and withdrawal syndrome (Vandrey et al., 2004)
- 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!"

# Estimated Drug Use and Dependence Amongst 15-45 Year-Olds in the US

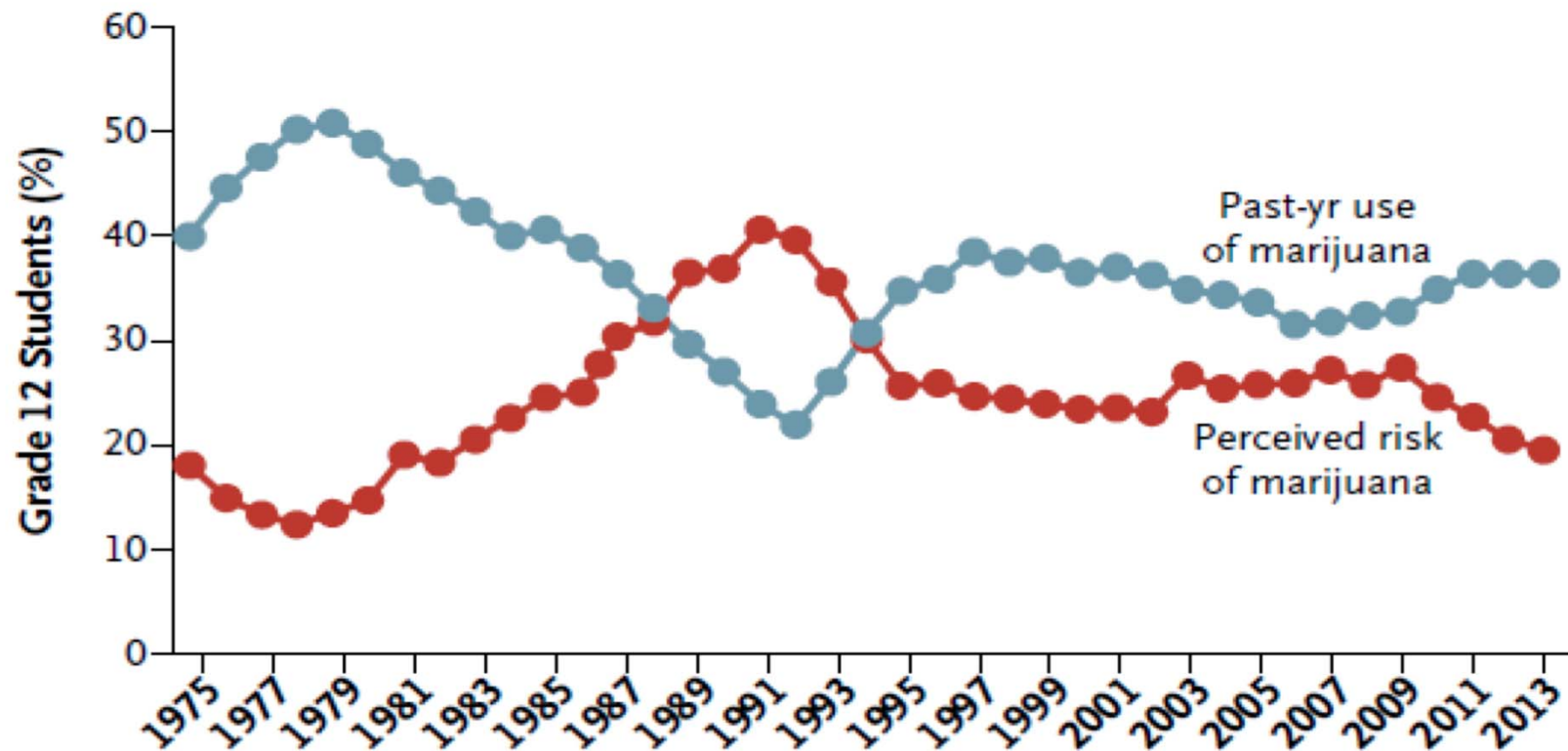
(Data from the National Co-morbidity Study; NCS)

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
<b>Cannabis</b>	<b>46.3</b>	<b>4.2</b>	<b>9.1</b>

Anthony, J.C. et al. (1994). Exp. Clin. Psychopharmacol. 2: 244-268.

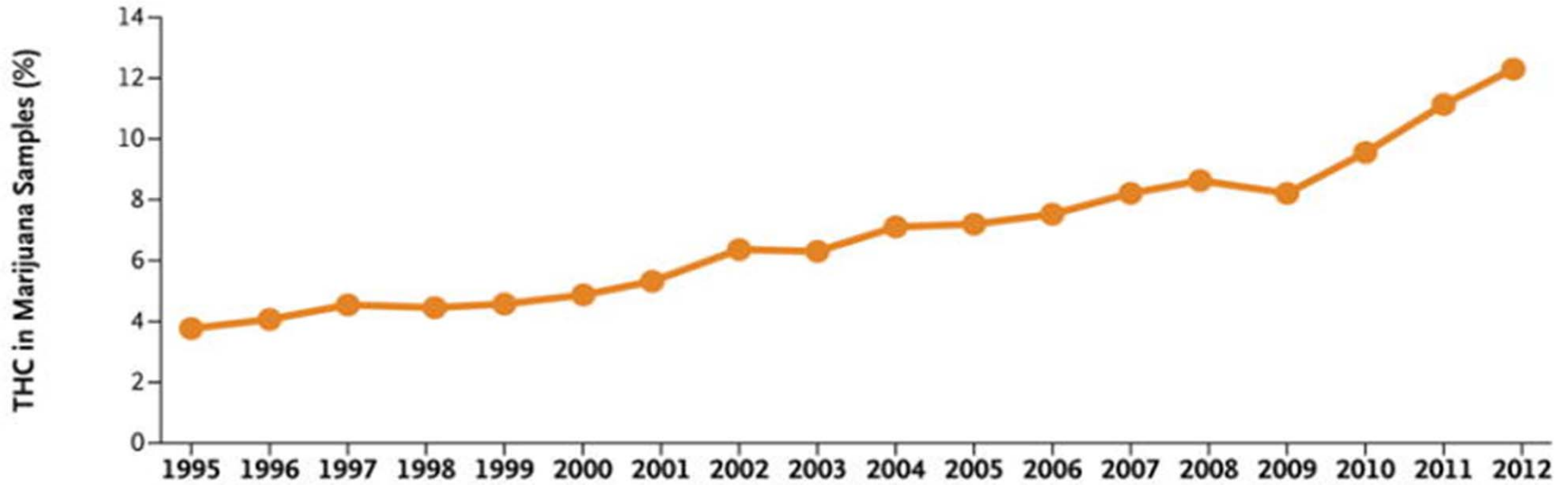
# Relationship Between Cannabis Use and Perceived Risk in Youth

A Correlation between Perceived Risk and Use

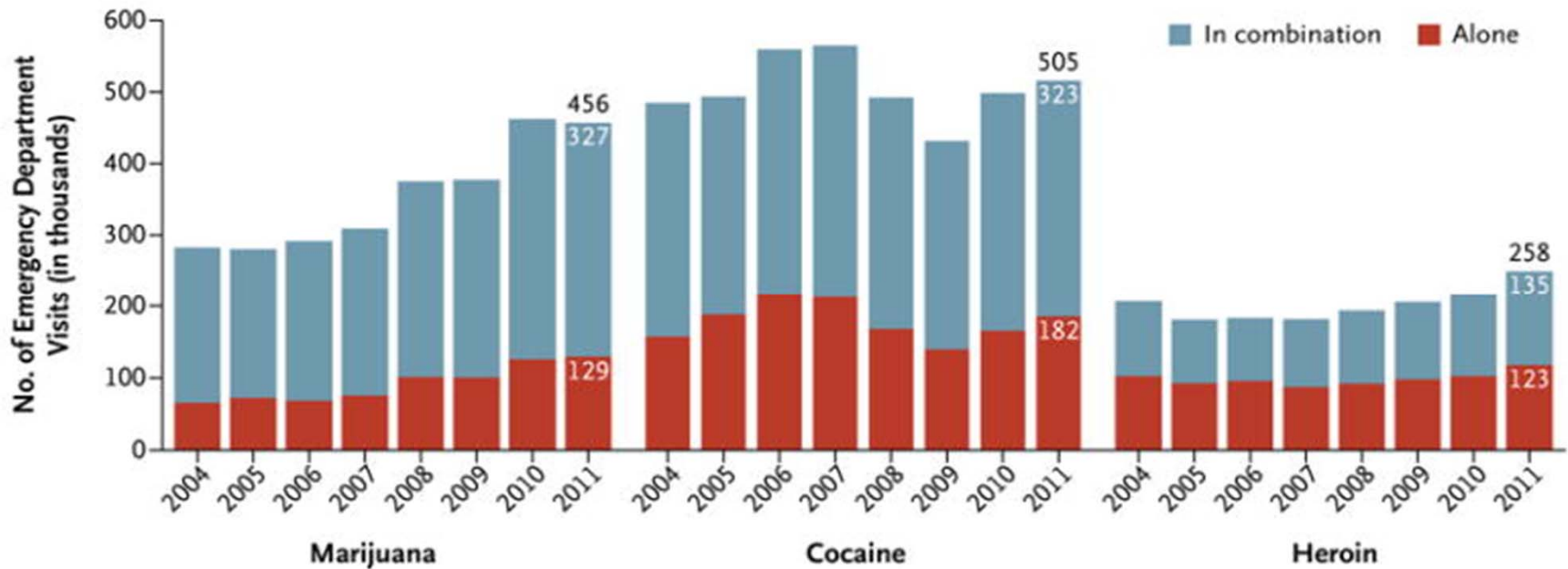


From: Monitoring the Future Study (MFS); reviewed in Volkow et al., 2014. NEJM

### A Potency of THC



### B Drug-Related Emergency Department Visits



# THC and CBD Content: 1975 and 2019

- In 1975: THC, 3%; CBD, 3%
- In 2019: THC, 25-35%; CBD <0.1%

Halah, M.P. et al. (2016). *Curr. Addict. Rep.* 4: 451-462.;

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

# Routes of Cannabis Use

## Smoked



## Vaporized

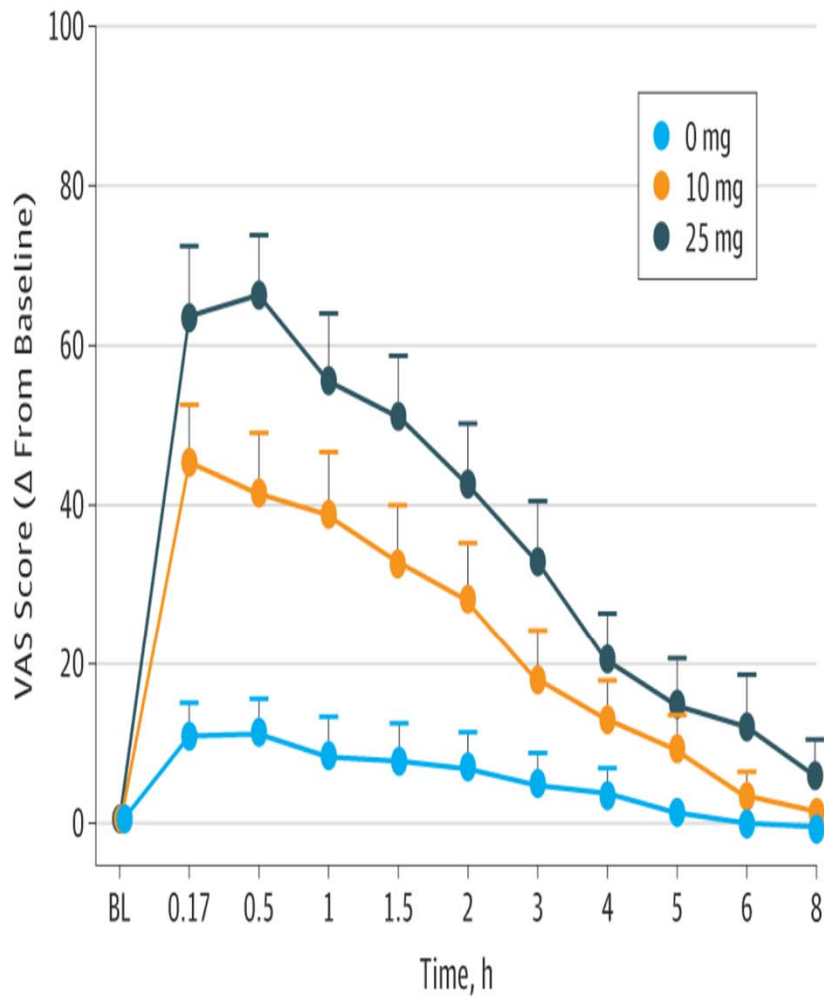


## Ingested

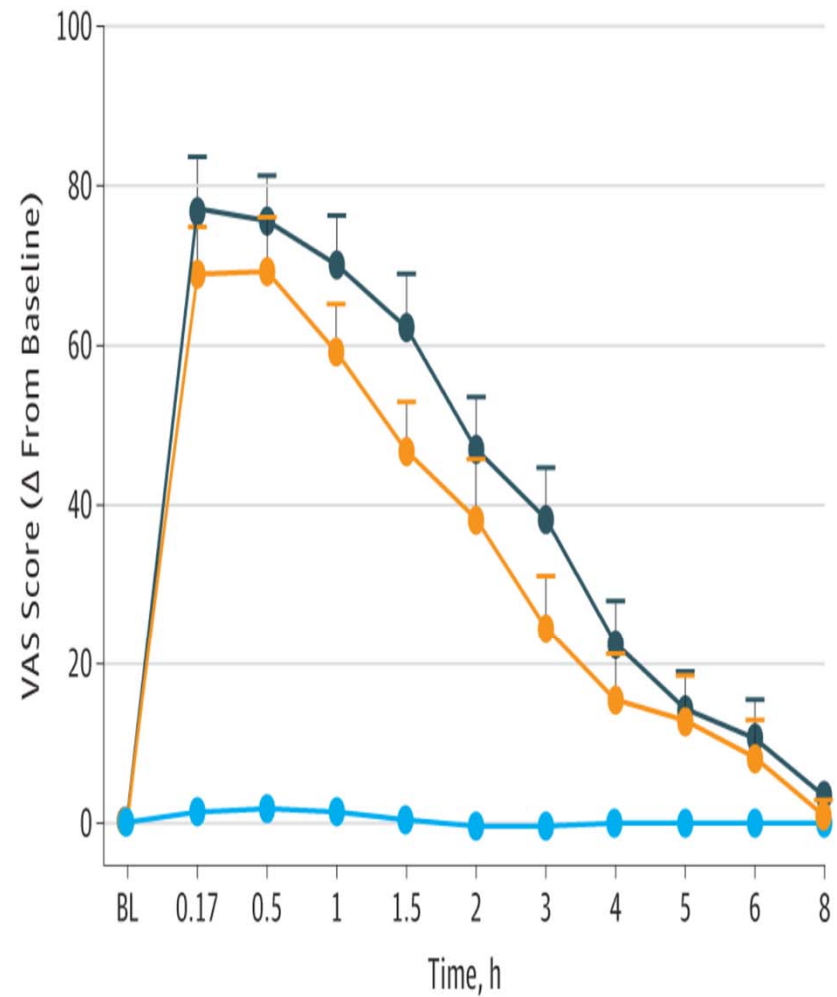


# Smoked versus Vaporized Cannabis – Subjective Effects

**A** Smoked



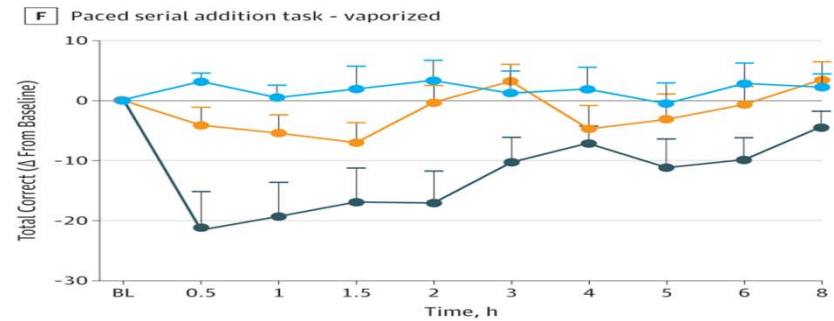
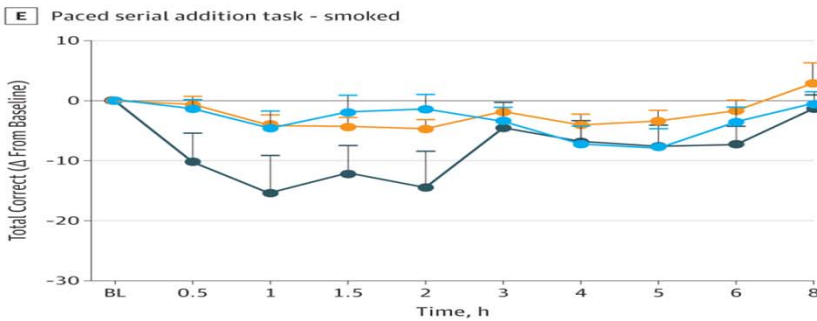
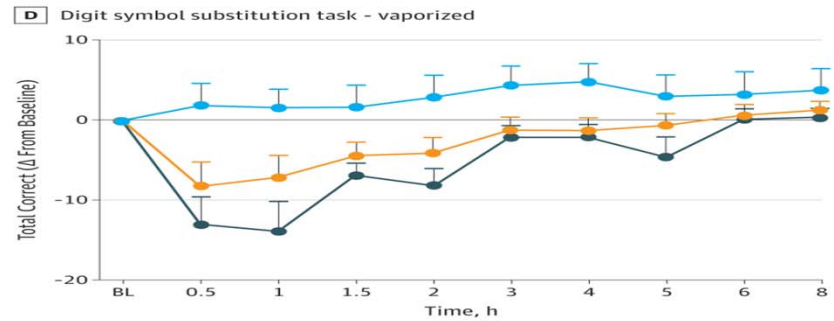
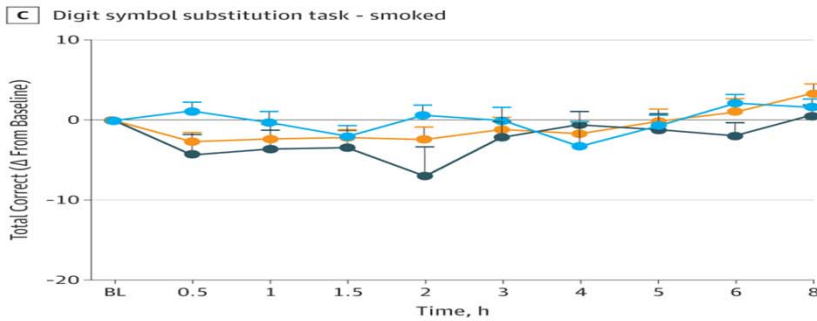
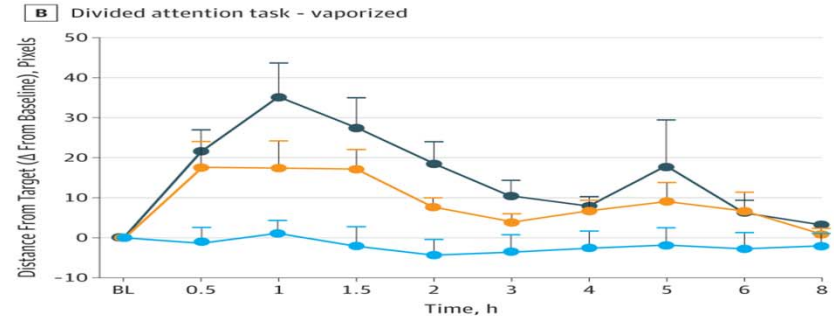
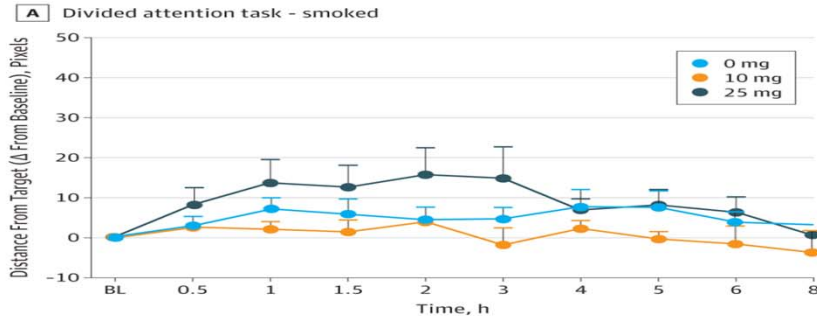
**B** Vaporized



**Spindle, T.R. et al. (2018). JAMA, in press.**



# Smoked versus Vaporized Cannabis – Cognitive Effects



Spindle, T.R. et al. (2018). JAMA, in press.

# Forms of Cannabis



# Hash oil (BHO), Shatter, Honey, Wax





1936



2018

<https://www.youtube.com/watch?v=sbjHOBjzhh0>

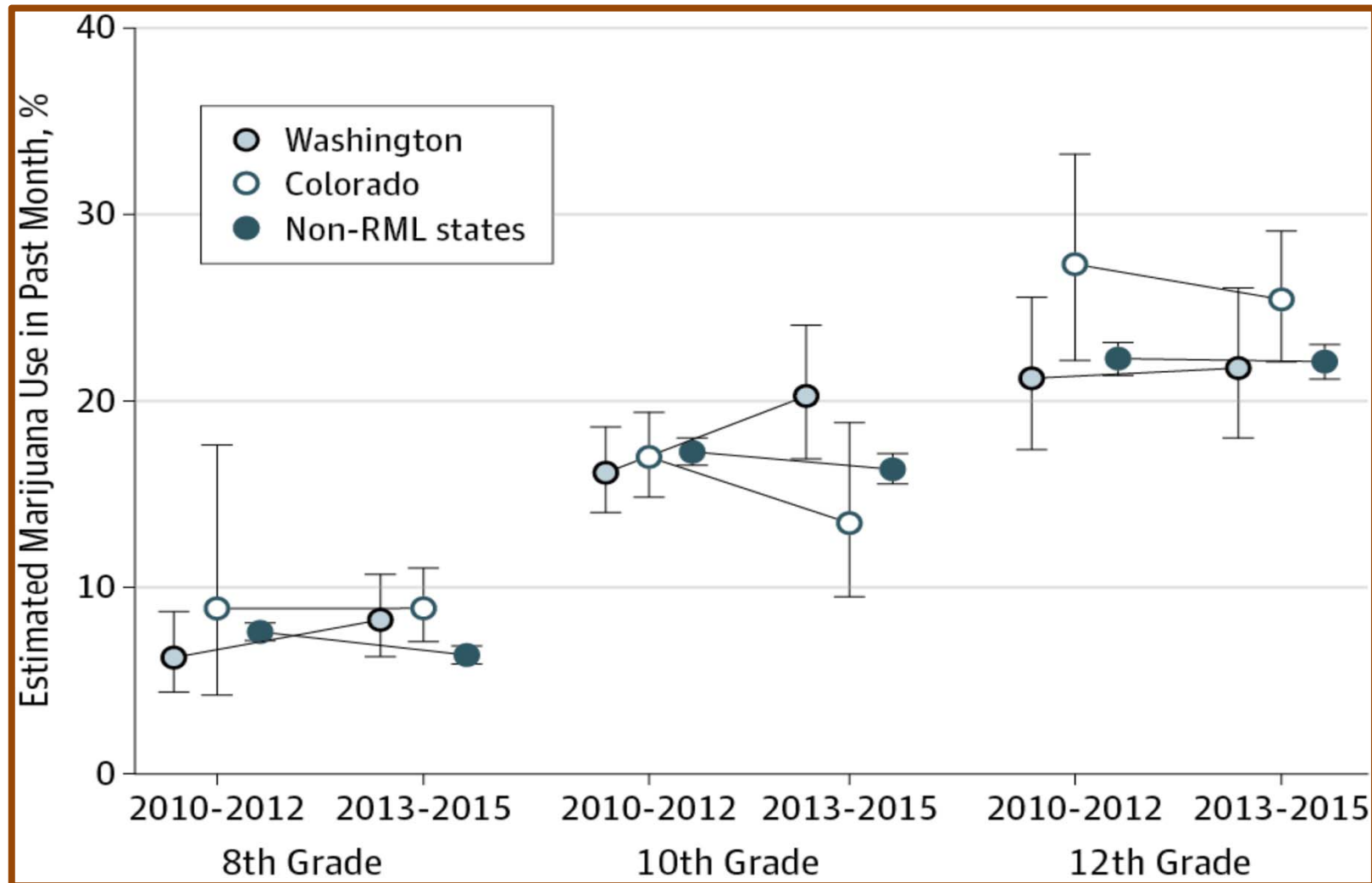
# Pros of Cannabis Legalization

- Shift burden of law enforcement away from minor crimes of trafficking and possession (including reducing disparities that impact on minorities)
- Easier access of the public to cannabis products – lessening of stigma associated with marijuana possession and use
- Reduce market share for “black market” cannabis products (including high potency cannabis, e.g. high THC content)
- Significant tax revenues (50/50 sharing between feds and provinces) could help the greater good (including prevention and treatment)

# Cons of Cannabis Legalization

- More permissive environment may reduce perception of cannabis risk.
- Potential to increase prevalence of cannabis use, especially in vulnerable subgroups (e.g. adolescents, mentally ill).
- May inadvertently increase access to higher potency forms of cannabis (with higher THC content) via the illegal market.

# From: Association of State Recreational Marijuana Laws With Adolescent Marijuana Use (N~150,000)



Cerda, M. et al., JAMA Pediatr. 2017;171(2):142-149.

# Therapeutic Evidence for Cannabis Use

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
<b>CLEAR HARMS</b>	--	<b>Schizophrenia</b> <b>Bipolar Disorders</b>

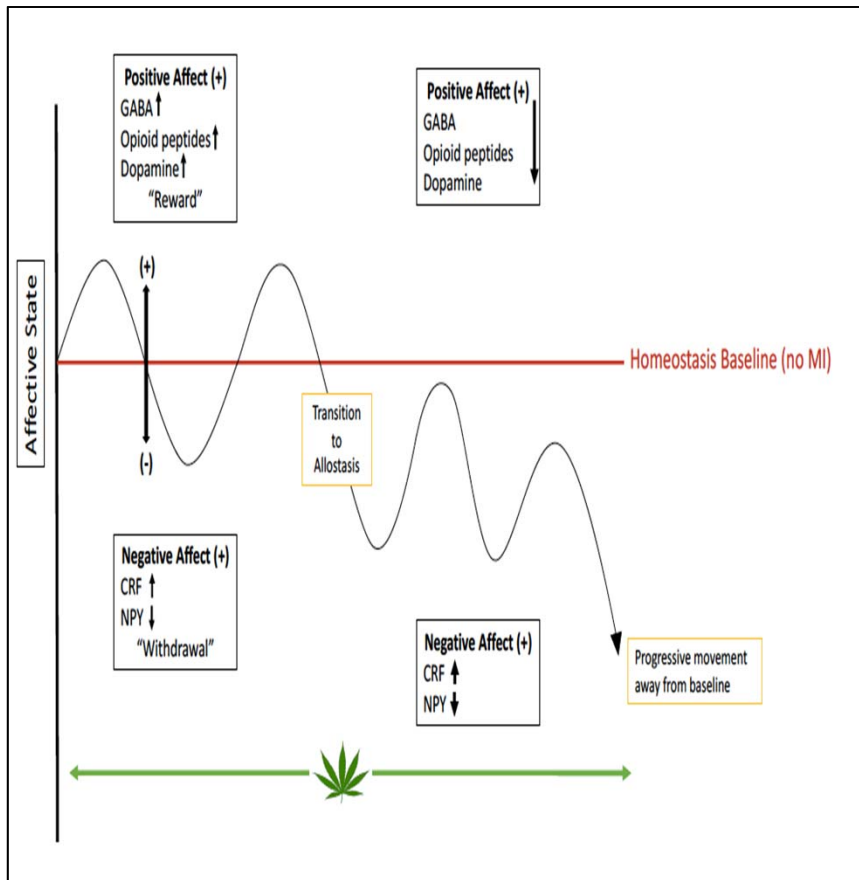
Hill, K.P. (2015) JAMA.313: 2474-2483; Halah, M.P. et al. (2016). Curr. Addict. Rep. 3: 450-462;  
George, T.P. et al., 2018. Can. J. Psychiatry. 63: 447-450.



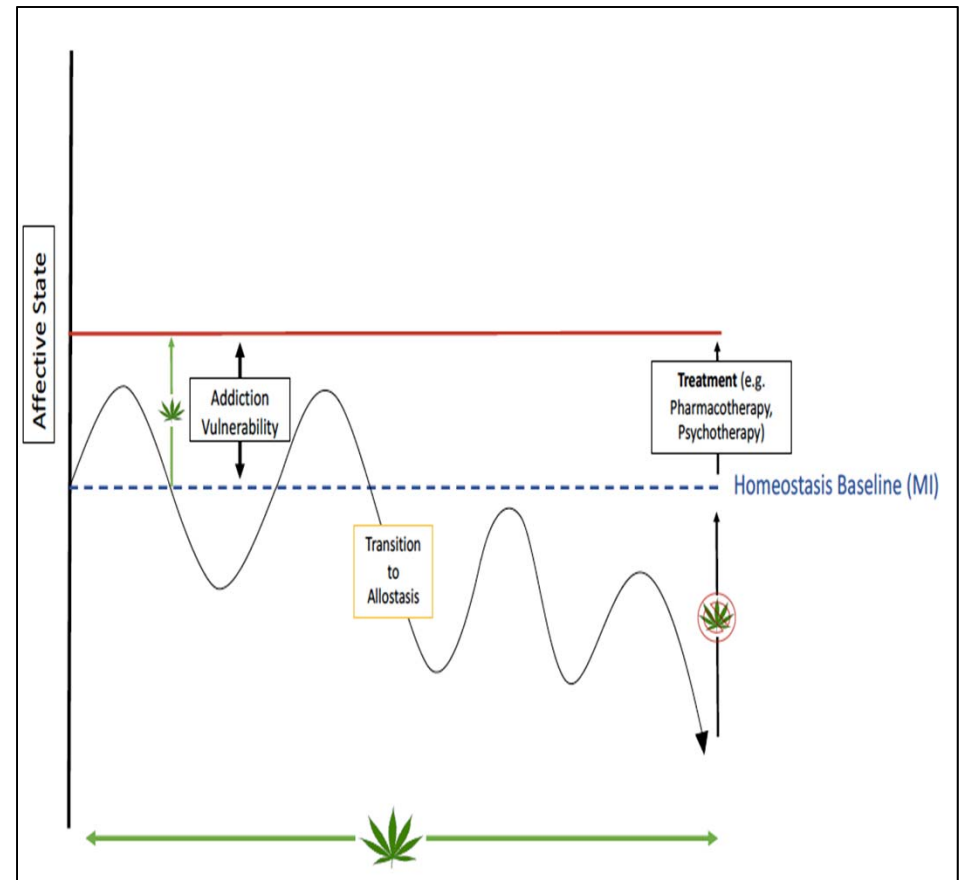
# Addiction Vulnerability and Allostasis Models Conceptualized for Cannabis Use Disorder (CUD) with and without Mental Illness



## CUD Alone



## CUD with Co-Occurring Mental Illness



Lowe, D.J.E. et al. (2019). Eur. Arch. Psychiat. Clin. Neurosci., in press.

# Recommendations of Canada's Working Group on Cannabis Legalization (Ware et al.)

- Legal access 18 years and above (*only AB and QC to follow, all others 19 years and above*)
- 30 grams personal possession dried cannabis
- 4 plants per household
- Clear Labelling 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)**

# Case Review: Cannabis-Induced Psychosis

- Jessica is a 19 year old UofT St. George's campus student who was admitted to the Early Psychosis Unit at CAMH in an acutely psychotic and agitated state. She is in her 2<sup>nd</sup> 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 all of her problems are due to the “hostile and competitive environment at UofT”, and that her pot smoking is the “only thing keeping me sane”.

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

<b>Primary psychosis (eg, schizophrenia)</b>	<b>Cannabis-induced psychosis</b>
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

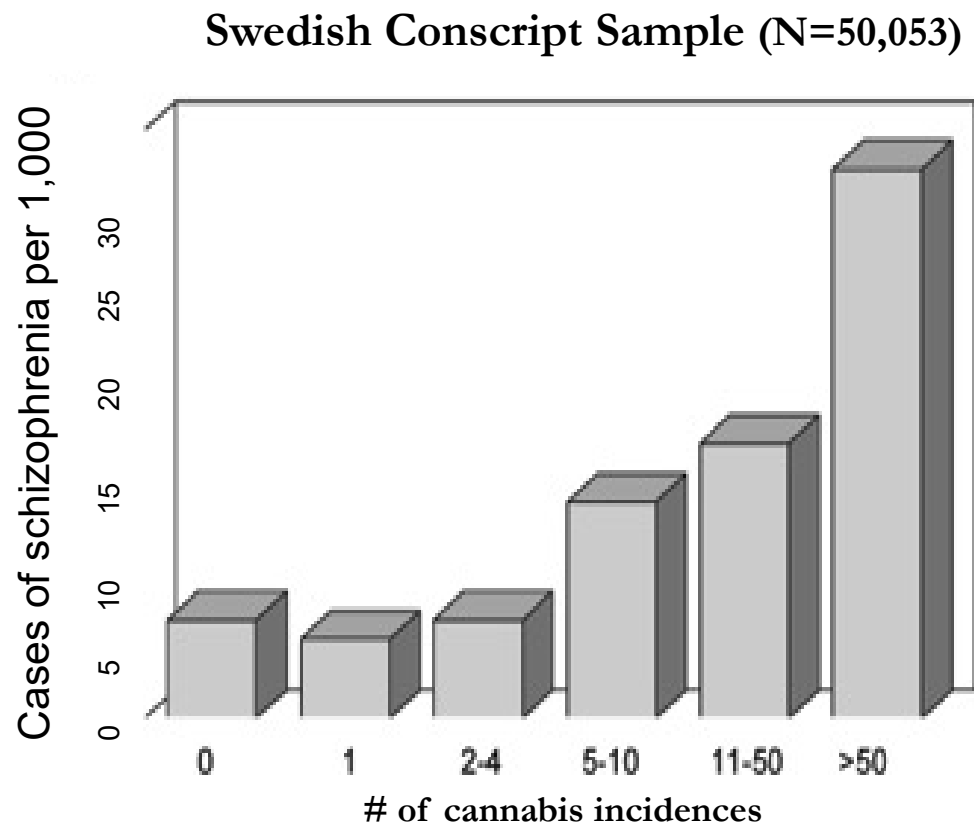
# Cannabis & Psychosis/Mood Disorders

- **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

Halah, M.P. et al. (2016). *Curr Addict. Rep.* 3: 450-462; Murray, R.M. et al. (2017). *Neuropharmacol.* 124: 89-104; Lucatch, A.M. et al. (2018). *Curr. Addict. Rep.* 5: 336-343.

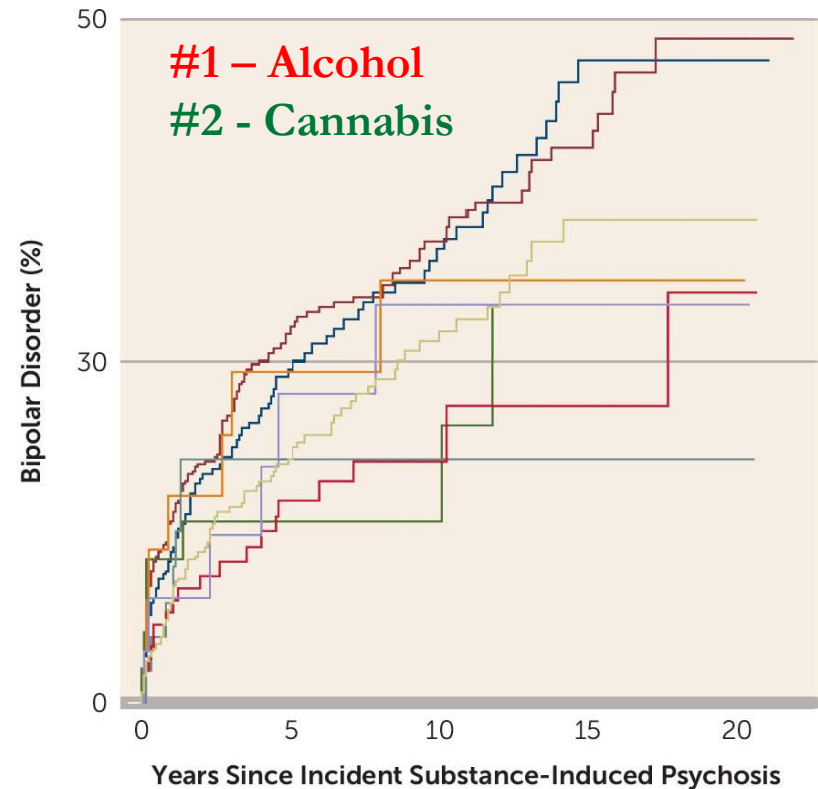
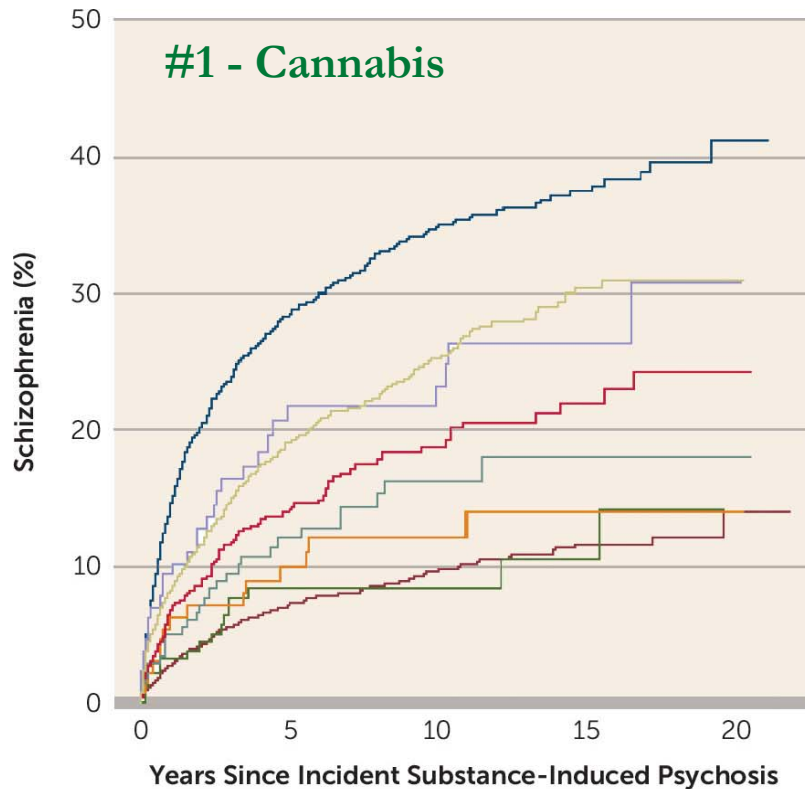
# Schizophrenia & Cannabis: Dose Effects

- Specificity to schizophrenia
- Dose-response relationship



**Cannabis use is associated with an increased risk of developing schizophrenia in a dose dependent fashion**

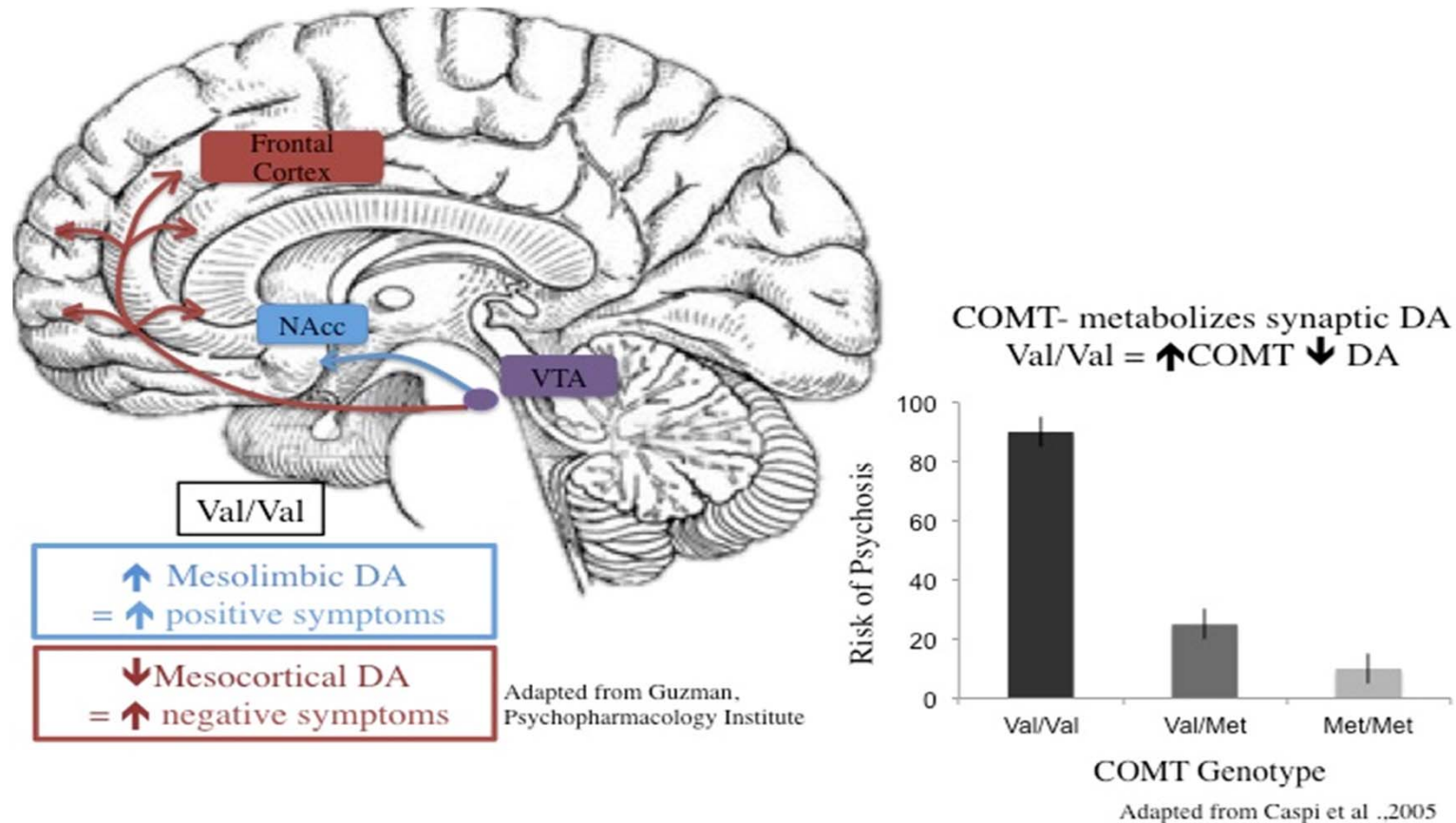
# Conversion to Schizophrenia or Bipolar Disorder in SIP: Cannabis May be the Most Problematic Drug



Starzer, M.S.K. et al. (2018). Am. J. Psychiatry. 175: 343-351.

# Cannabis, COMT and Psychosis

(Caspi et al., 2005)



**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.

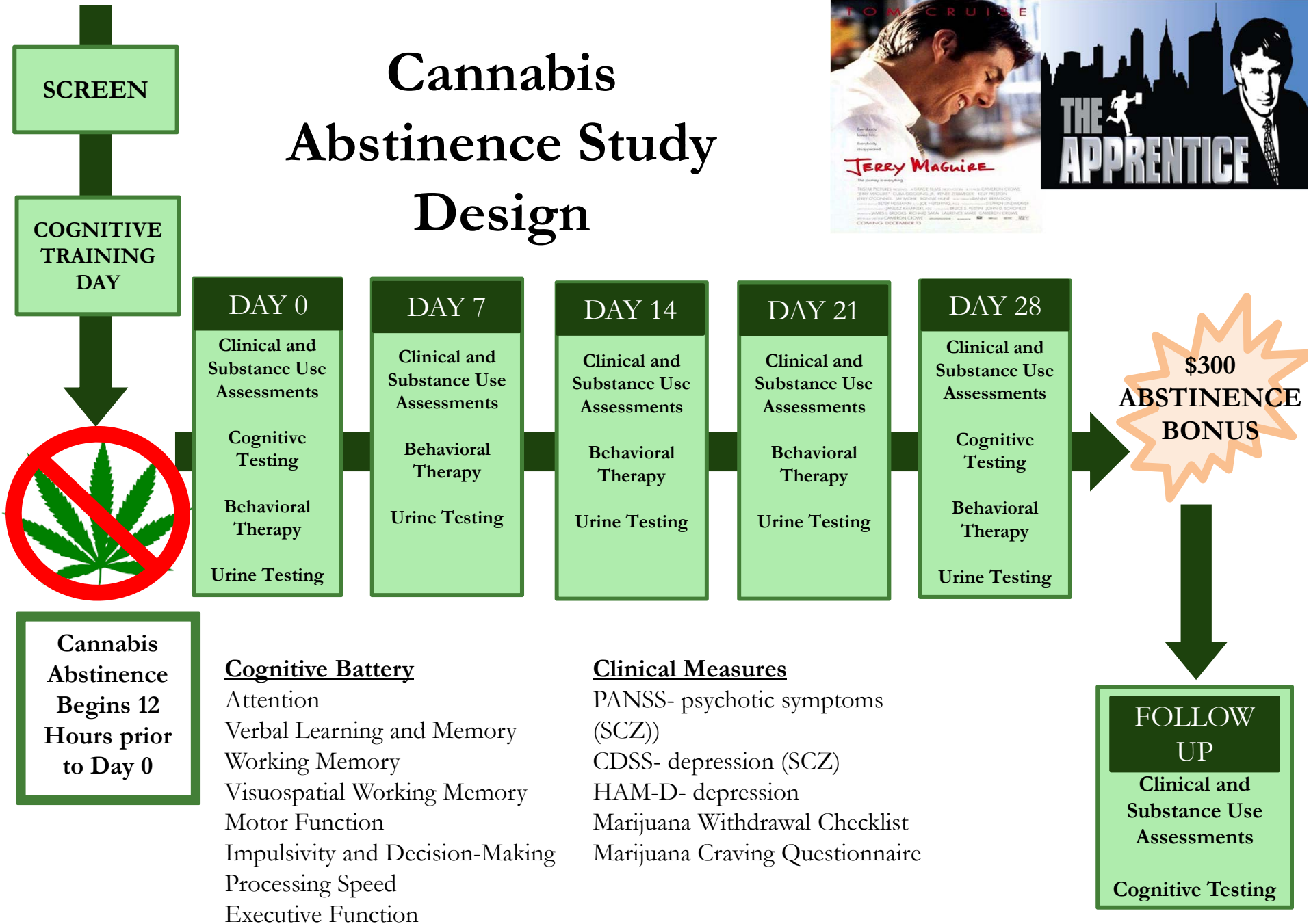


# Is there brain functional recovery with sustained cannabis abstinence in people with schizophrenia?



**Rachel A. Rabin, Ph.D.**

# Cannabis Abstinence Study Design



# Was the Abstinence Paradigm Successful?



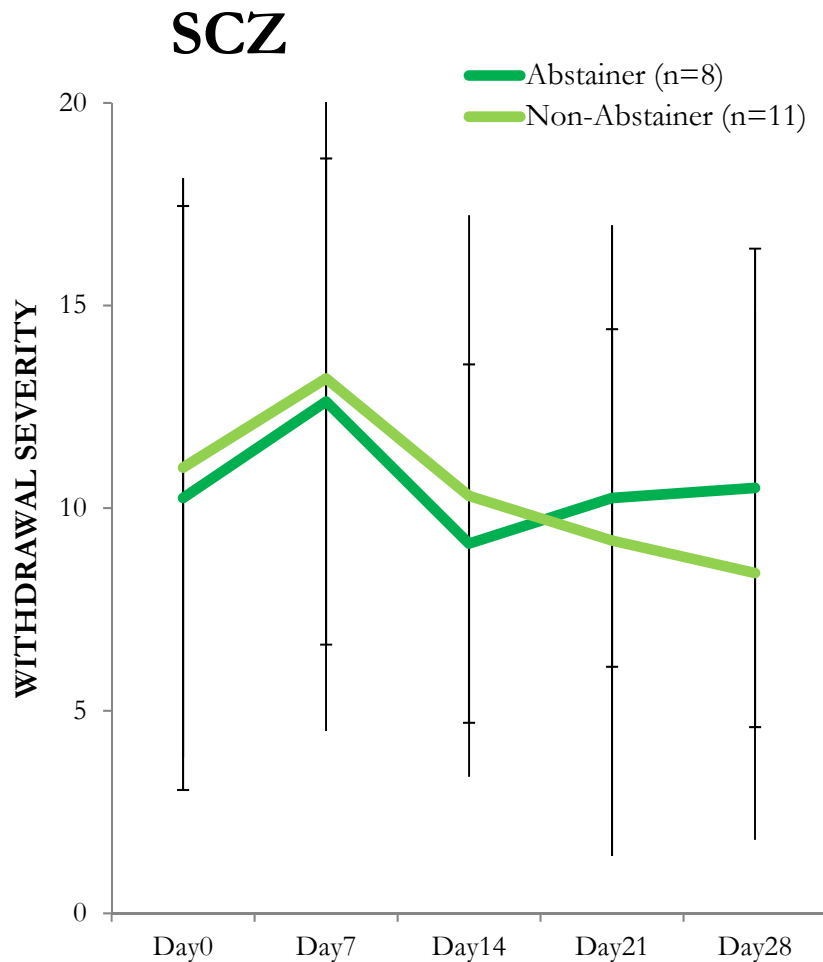
# Abstinence Results

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%

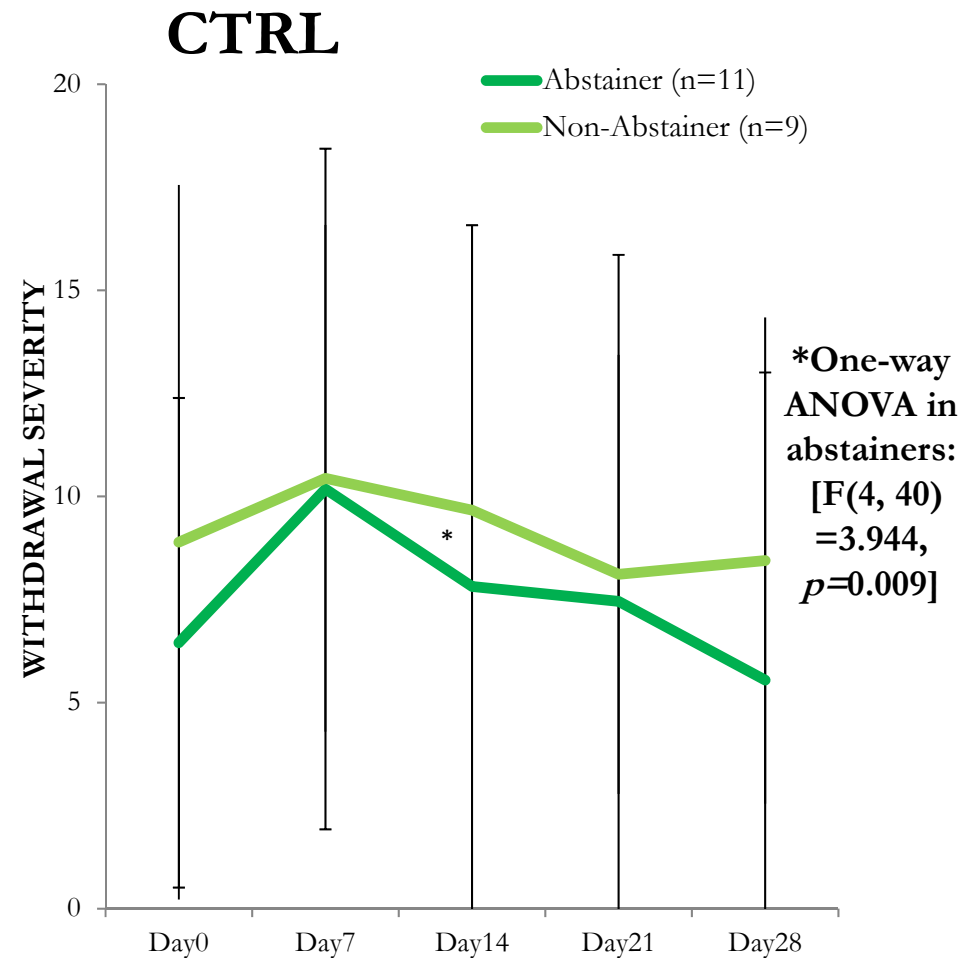
There was no statistical difference in rates of abstinence between patients and controls

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

# Withdrawal Symptoms



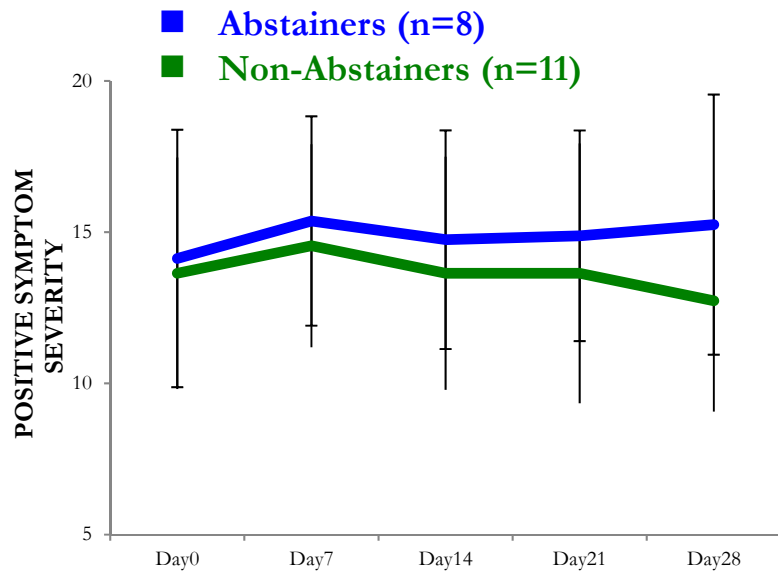
Time; [F(4, 68) = 1.607,  $p=0.182$ ]; Time x group; [F(4, 68) = 0.357,  $p=0.838$ ]



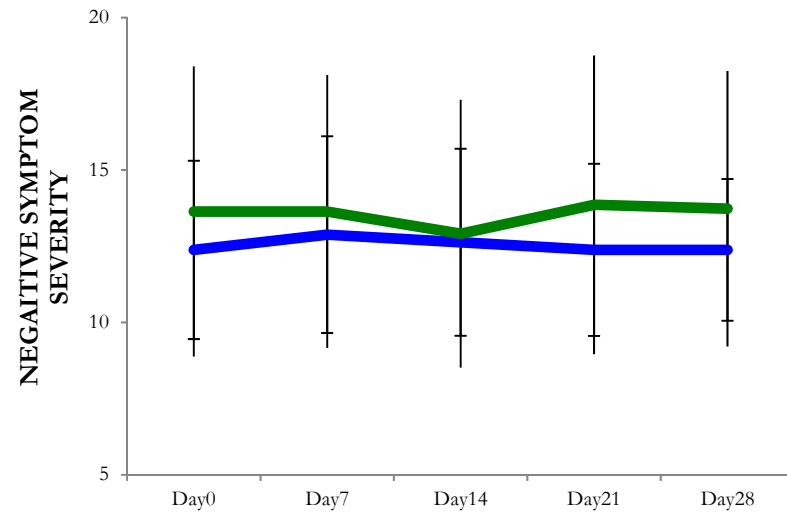
Time; [F(4, 72) = 2.172,  $p=0.080$ ]; Time x group; [F(4, 72) = 0.420,  $p=0.793$ ]

# Effects of Cannabis Abstinence on Psychotic Symptoms

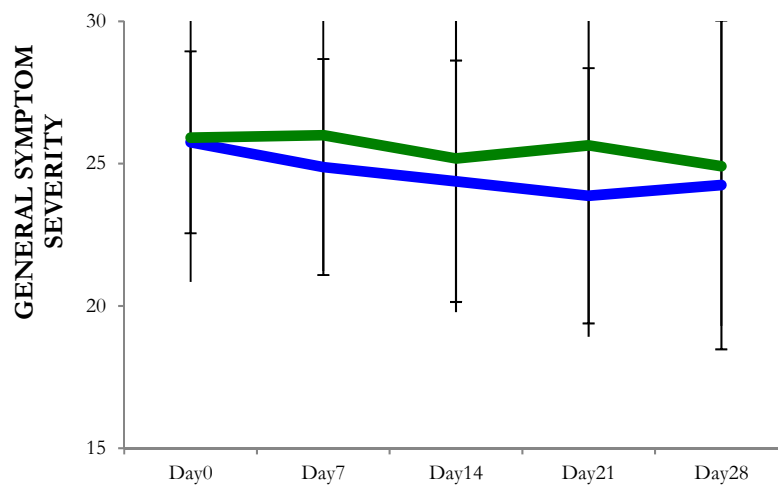
Rabin, RA et al. (2018). Schizophr. Res. 194: 55-61.



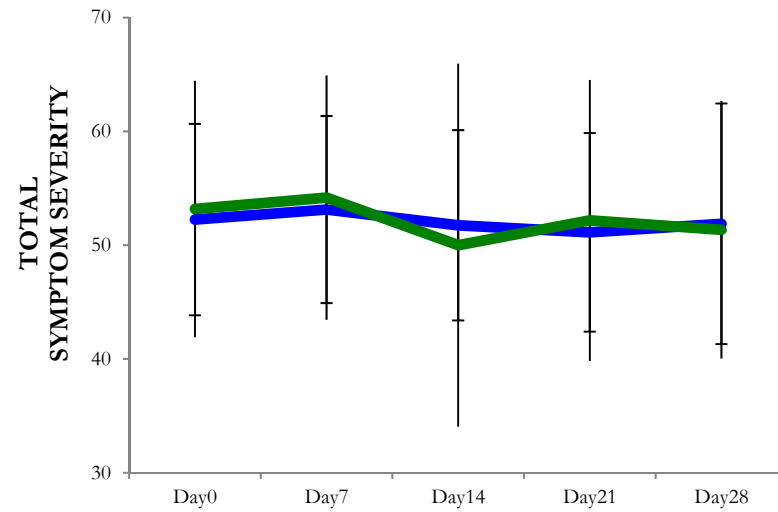
$F(4, 68) = 1.430, p = 0.234$



$F(4, 68) = 0.882, p = 0.480$

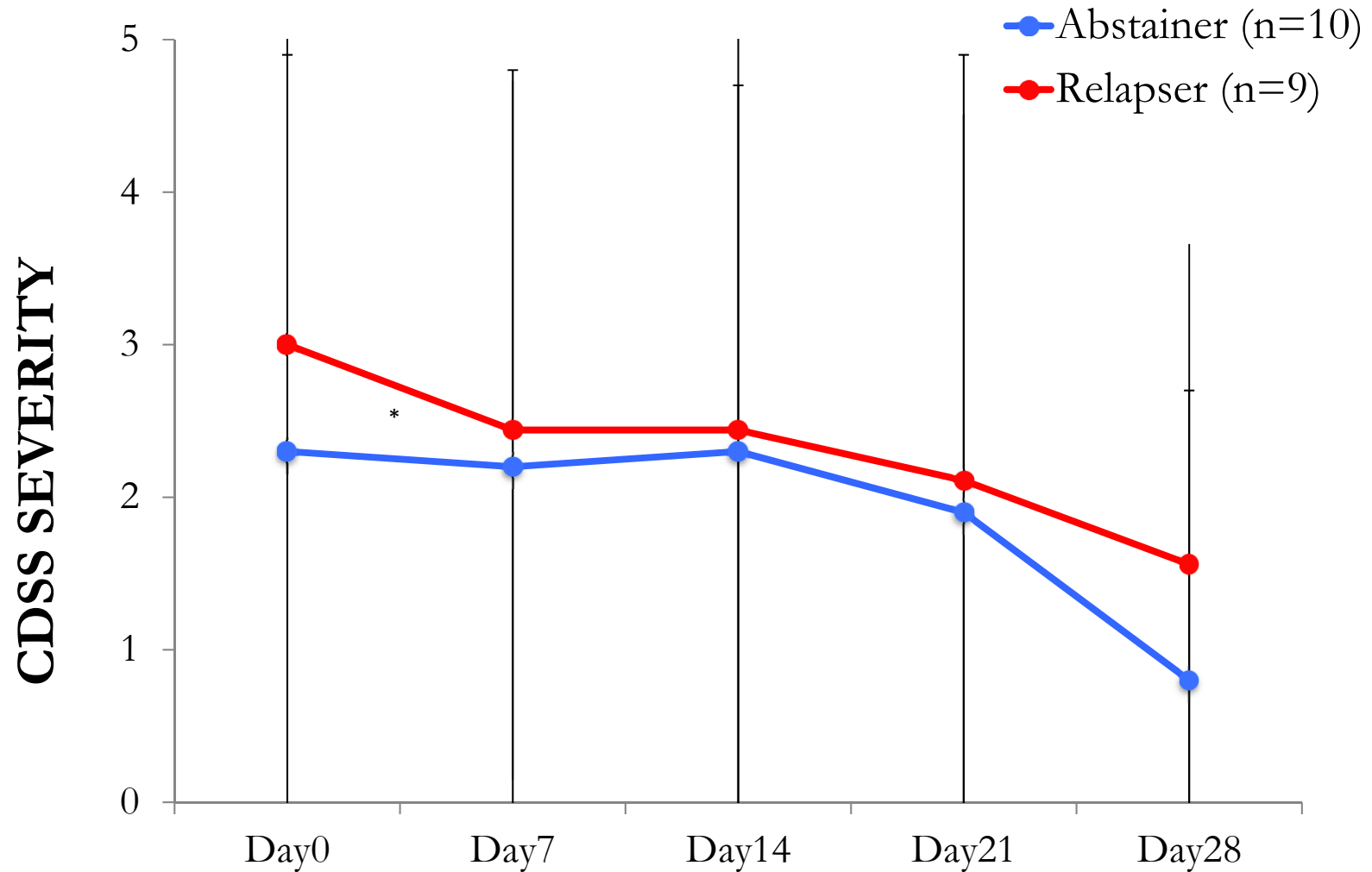


$F(4, 68) = 1.229, p = 0.307$



$F(4, 68) = 1.112, p = 0.358$

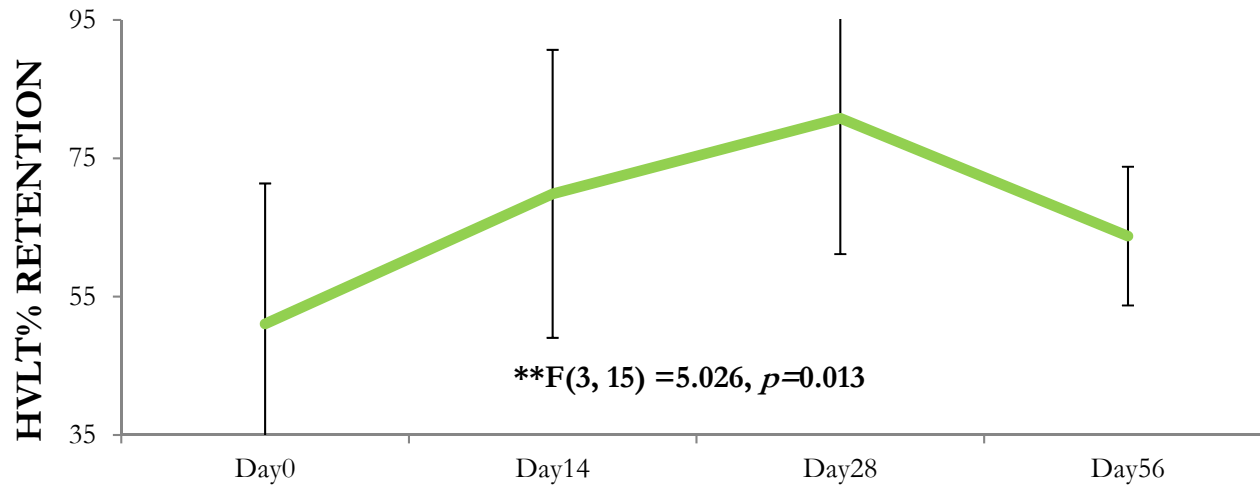
# Effects of Cannabis Abstinence on Depressive Symptoms in Schizophrenia



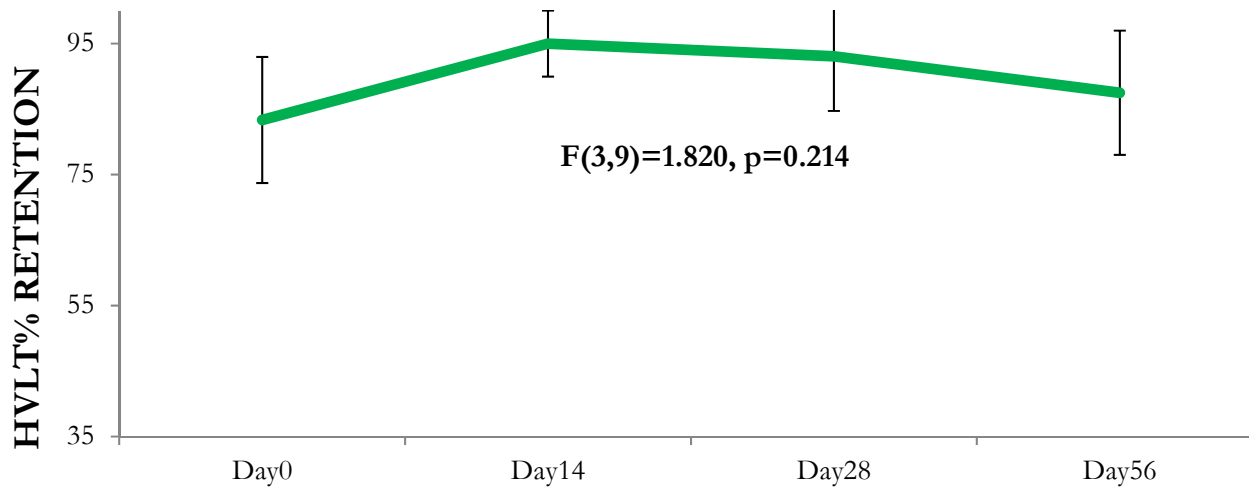
Rabin, R.A. et al.(2018). Schizophr. Res.. 194: 55-61.

# Verbal Memory Improved with Abstinence and Worsened with Relapse in SCZ

SCZ: N=6



CTRL: N=4



Rabin, RA et al. (2017). Neuropsychopharmacology. 42: 2259-2271.

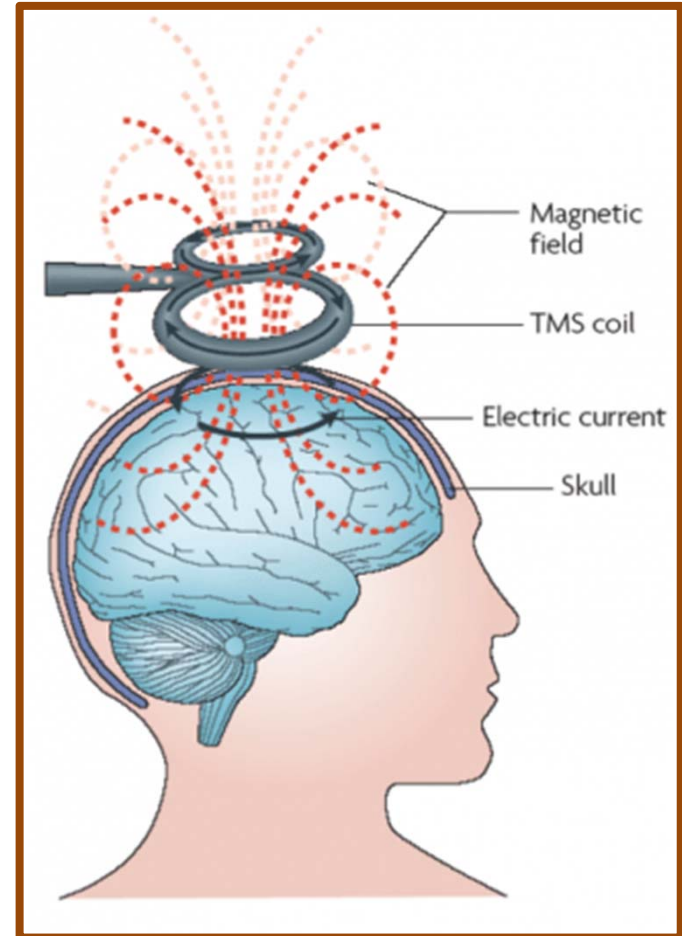


# Treatment

- **Behavioural:**
  - Motivational interviewing (MI)
  - Cognitive-Behavioural therapy (CBT)
  - Contingency management (CM)
- **Pharmacotherapies – none approved**
  - Cannabinoids- Marinol (Dronabinol); Cesamet (Nabilone); CB1 Antagonists (e.g. Rimonabant)
  - N-Acetylcysteine (NAC) – *Gray et al (2012). Am. J. Psychiatry.*
  - Antidepressants (bupropion, nefazadone)/Mood Stabilizers (valproate)
  - Nabiximols (Sativex; THC/CBD, 1:1) – *Allsop et al., 2016; Trigo et al., 2018*
  - FAAH Inhibitors (*D'Souza, D.C. et al., 2019. Lancet Psychiatry. 6: 35-42*)

# Repetitive Transcranial Magnetic Stimulation (rTMS)

- Stimulates the cortex by trains of magnetic pulses
- Uses frequencies ranging from 1 to 50Hz
- rTMS has recently been used to treat neuropsychiatric disorders (e.g. depression, schizophrenia, Parkinson's disease)

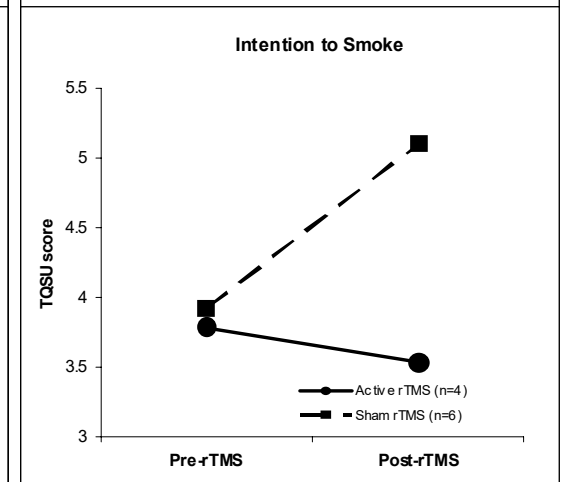
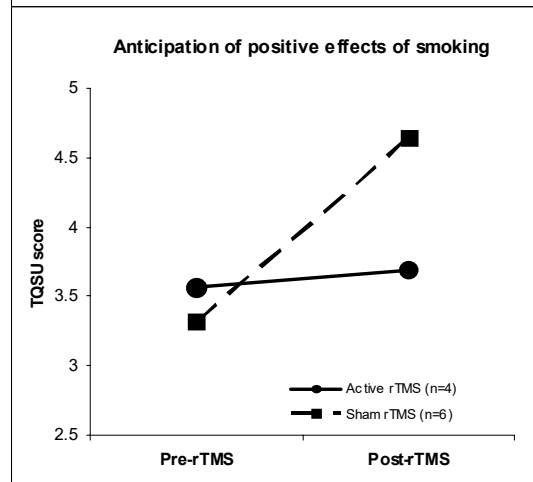
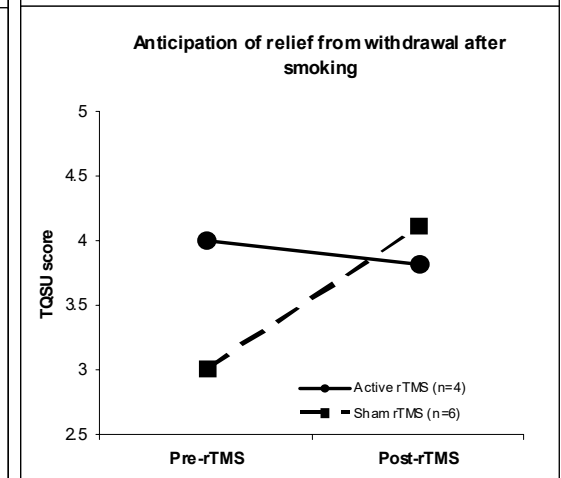
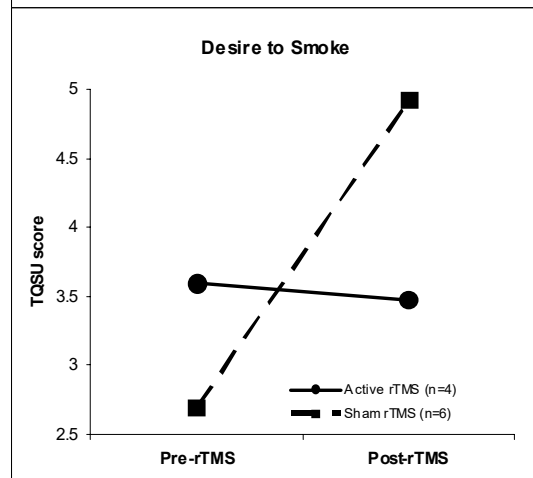
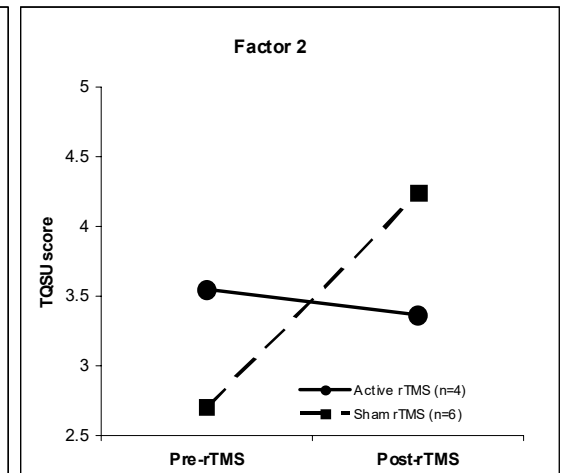
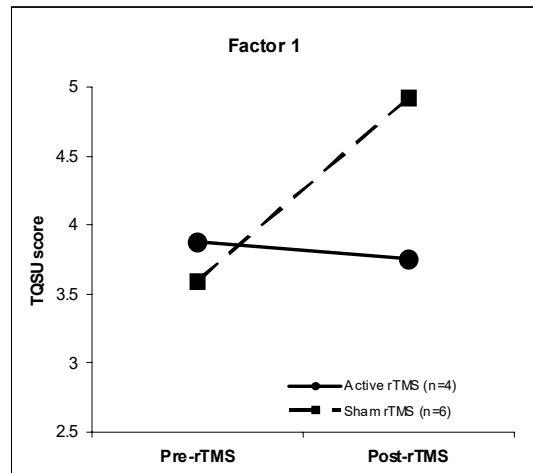


# Summary of Brain Stimulation Treatment Studies in SUDs

Stimulation Method	Repetitive Transcranial Magnetic Stimulation (rTMS)	Transcranial Direct Current Stimulation (tDCS)	Deep Brain Stimulation (DBS)
Tobacco	+++	++	+/-
Alcohol	+	+	+/-
Cannabis	--	+	--
Stimulants (Cocaine, Methamphetamine)	+++	+++	--
Opioids	--	--	+/-

Coles, A.S. et al. (2018). Am. J. Addict. 27: 71-91.

# Repetitive Transcranial Magnetic Stimulation (rTMS) reduces tobacco cravings in patients with schizophrenia



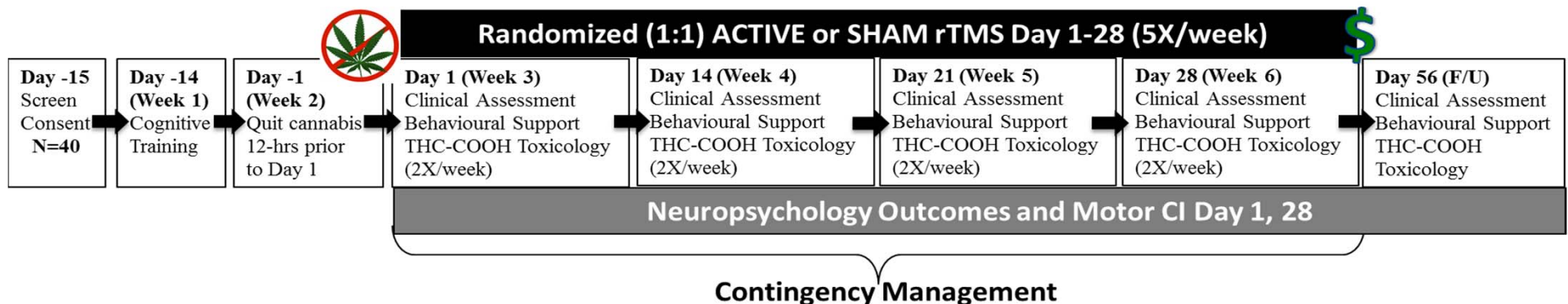
# High-Frequency rTMS (20Hz) for Cannabis Use Disorder in Schizophrenia (NIDA Grant: 1R21-DA-043949)

- **PI: Tony P. George, M.D., FRCPC** (ClinicalTrials.gov Registration – [NCT03189810](#))
- Funded by Astrid H. Flaska Foundation (2017-2019) and NIDA grant R21-DA-043949; 9/15/17-7/31/19)
- **Leads: Karolina Kozak, M.Sc., Ph.D. Candidate** and **Darby Lowe, B.Sc., Master's Candidate, UofT IMS**



## DESIGN:

- 5x/week HF rTMS bilaterally to DLPFC for 4 weeks.
- N=40 Subjects, ages 18-55, meet criteria for CUD, moderate to severe, schizophrenia diagnosis on SCID-5.
- Monetary incentives for rTMS session attendance
- **N=12 subject randomized to date**



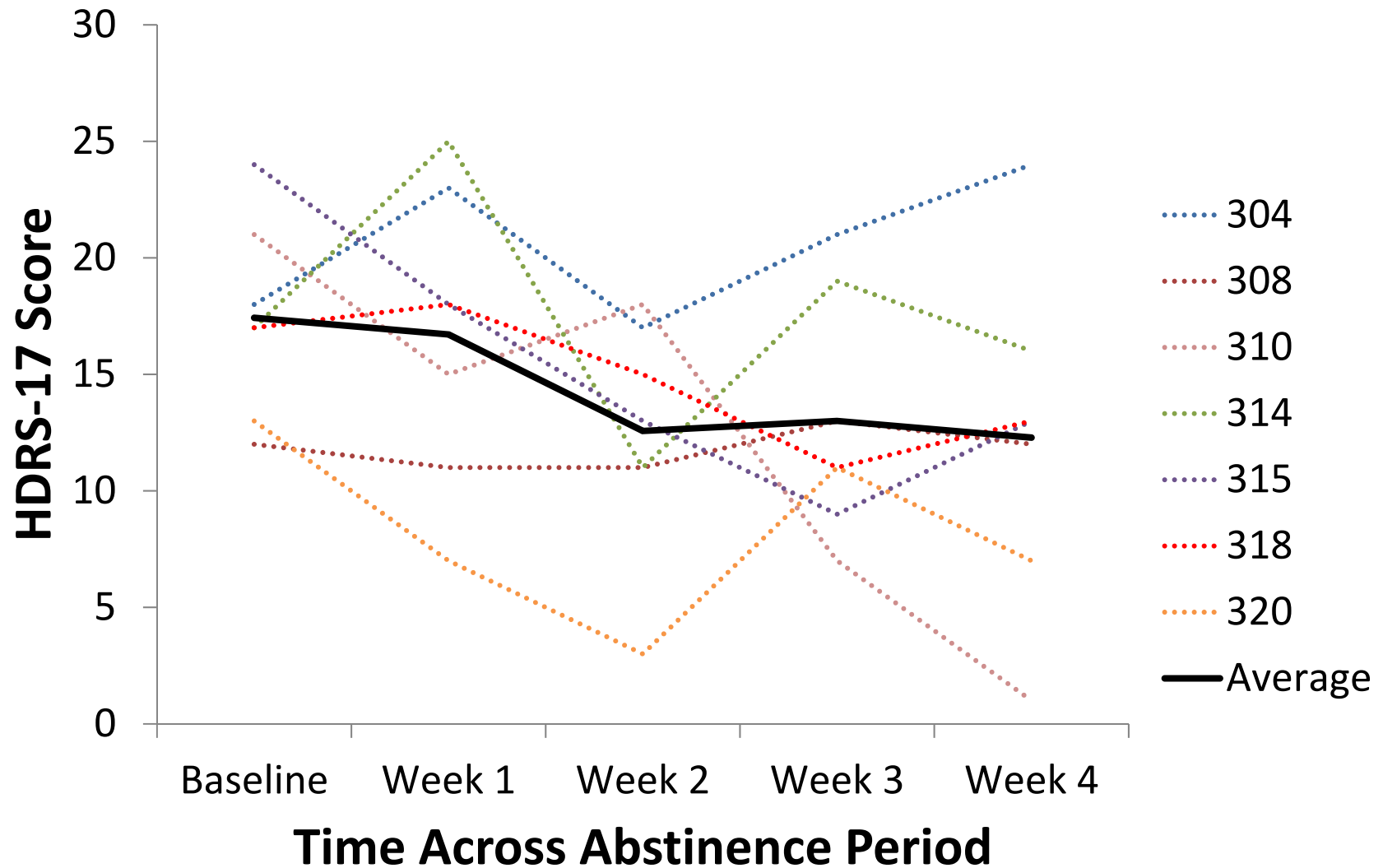
# Cannabis Abstinence in Major Depression Study

- **Cannabis Abstinence in Major Depressive Disorder (MADCAN)**
  - **Lead: Aliya Lucatch, HB.Sc. – IMS M.Sc.**  
Thesis, in progress
  - Subjects with MDD and CUD will attempt 28 days of cannabis abstinence
  - \$300 contingent bonus at Day 28 IF subjects report cannabis abstinence confirmed by biochemical testing (THC-COOH level <20 ng/ml performed using GC/MS/MS)
  - Primary outcomes would be mood and anxiety symptoms, anhedonia (SHAPS/PRL Task) and cognition.
  - N=8 subjects completed to date.



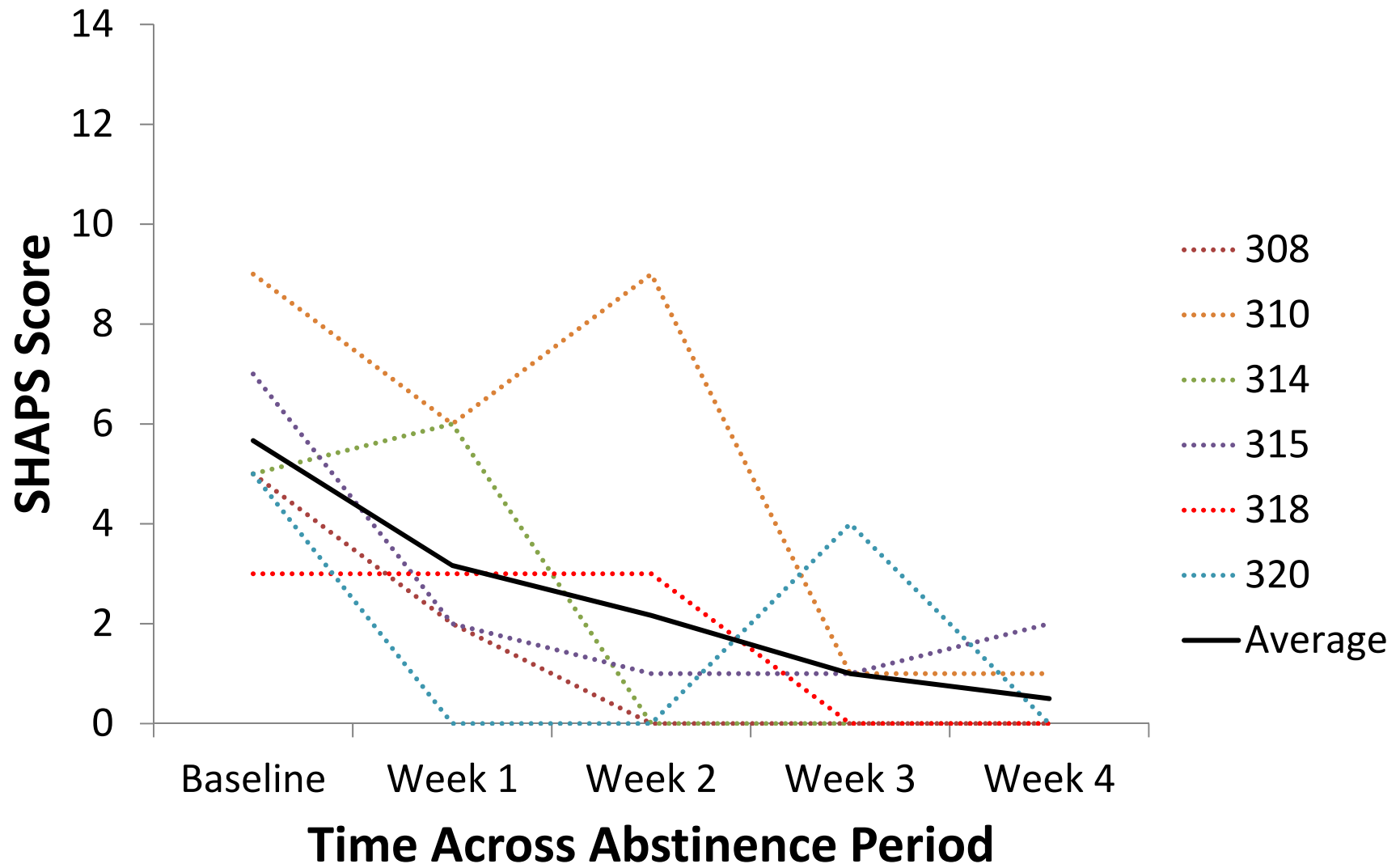
**Aliya Lucatch**

# Changes in Depressive Symptoms (HDRS-17) with 28-days of Verified Cannabis Abstinence



Lucatch, A.M. et al. (2018). ACNP Conference. Hollywood, FL

# Changes in Anhedonia (SHAPS) Scores with 28-days of Verified Cannabis Abstinence



Lucatch, A.M. et al. (2018). ACNP Conference, Hollywood, FL



# Cannabis Abstinence in Bipolar Disorder Study

- **Cannabis Abstinence in Bipolar Disorder (BICAN)**

- Study Leads: Alexandria Coles, B.A. and Julia Sasiadek, B.A.
- Bipolar subjects with CUD will be randomly assigned to a contingent reinforcement (CR) versus non-contingent reinforcement (NCR) groups.
- We expect much higher rates of biochemically-verified Day 28 cannabis abstinence in the CR versus NCR groups.
- Primary outcomes would be mood symptoms (depression and hypomania) and cognition.
- Enrollment begins January, 2019



Alex Coles



Julia Sasiadek

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

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and Franco J. Vaccarino, PhD, FCAHS<sup>4</sup>

## Keywords

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

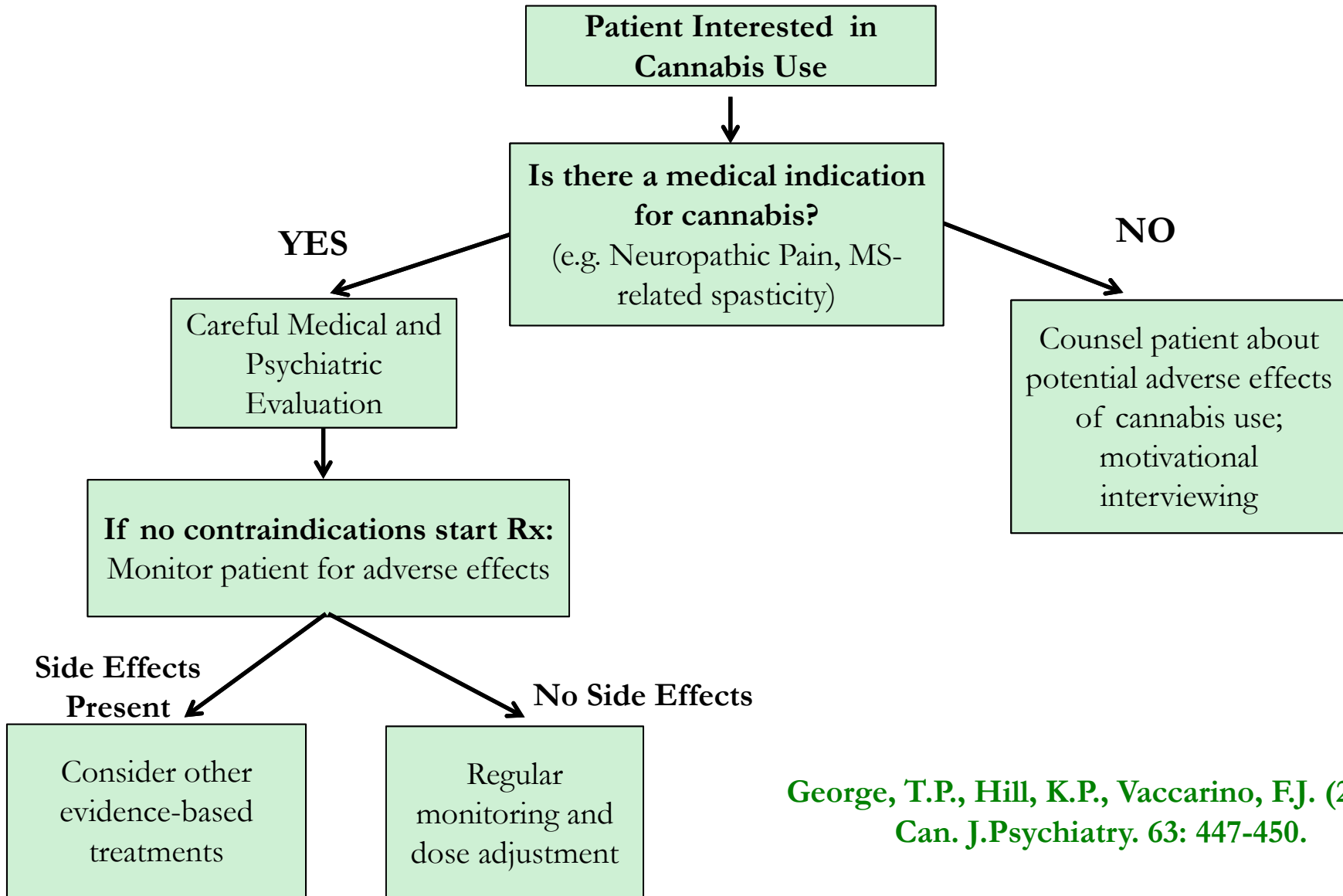
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# Caveat “H-Emptor”- Six Recommendations

1. National Strategy for Public Education on Cannabis and Harms X
2. Limits on THC Potency and Clear Product Labeling Post-Legalization ✓
3. Evidence-Based Age Limit for Recreational Cannabis Use X
4. National Surveillance Strategy Pre- and Post-Legalization X
5. Developing Treatment Capacity for Problematic Cannabis Use – with Special Emphasis on Youth and People with Mental Illness X
6. Education and Training for Physicians and Other Healthcare Providers on the Benefit and Harms of Cannabis X

# A Guide for Physicians and Cannabis Using Patients



George, T.P., Hill, K.P., Vaccarino, F.J. (2018).  
Can. J.Psychiatry. 63: 447-450.

# In Summary

- **The Good:** Legalization will bring many benefits particularly from a consumer access and law enforcement perspective. And we have the technology to treat problematic cannabis use (e.g. CUD).
- **The Bad:** Evidence indicates that there are significant harms of cannabis, especially in youth and the mentally ill. Moreover, scientific evidence to support the therapeutic benefits of cannabis is modest.
  - **Caveat H-Emptor!** (George, T.P. et al., 2018. Can. J. Psychiatry. 63: 447-450).
- **The Challenging:** How do we practically implement cannabis legalization and regulation so that the well-being and safety of Canadians is ensured?

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