

Reefer Madness: Science, Policy, Healthcare and Cannabis in 2020



Ryan Vandrey, PhD

Johns Hopkins University School of Medicine

Disclosures

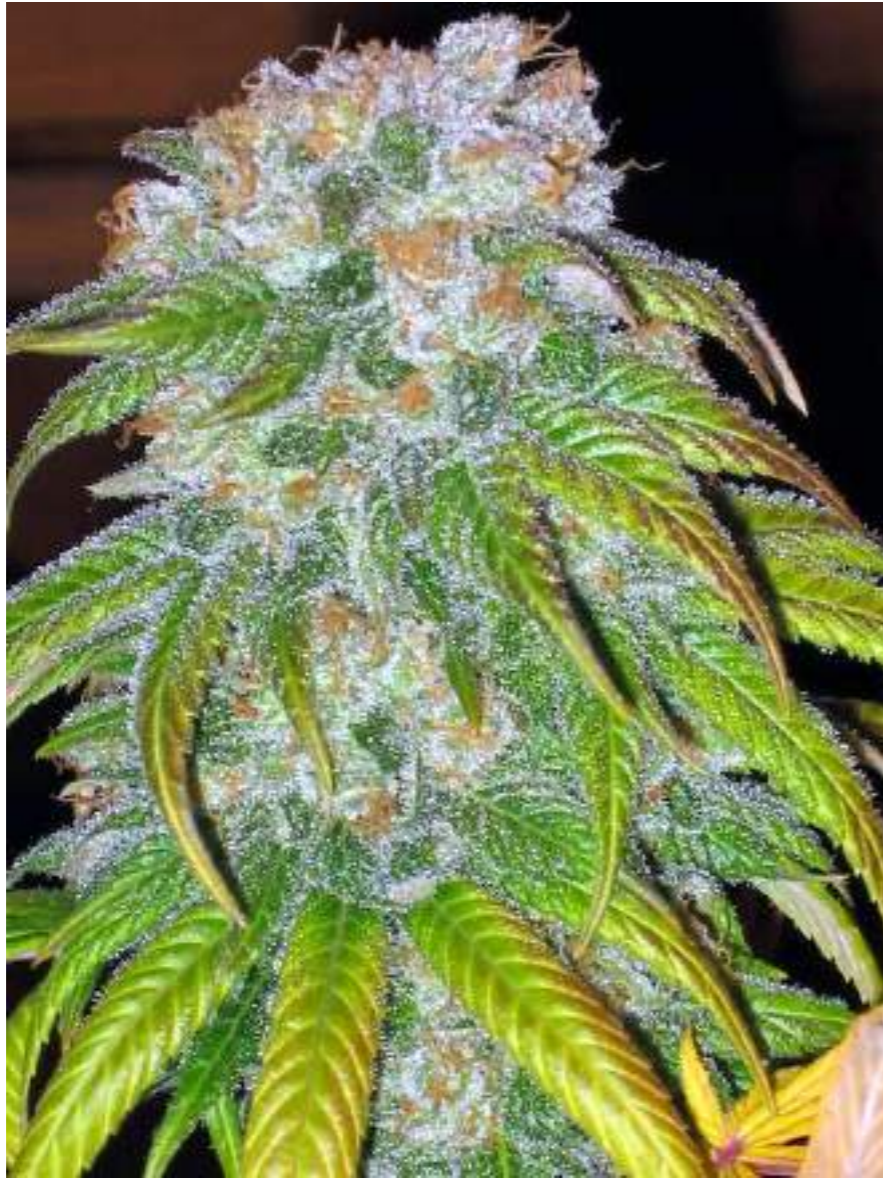
- **Paid consultant to Canopy Health Innovations**
- **Advisory board member for FSD Pharma, Present Life Corporation**



What Is Cannabis?



This is Cannabis Right?



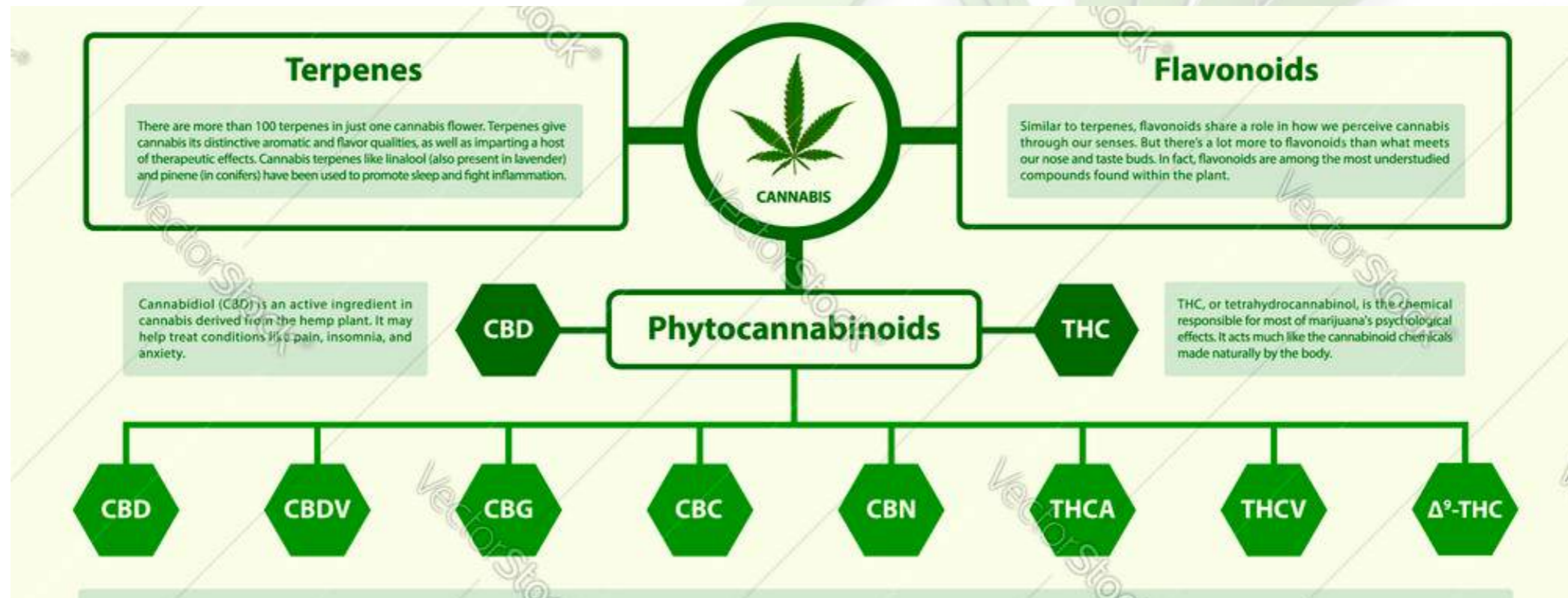
Retail Products in the U.S.



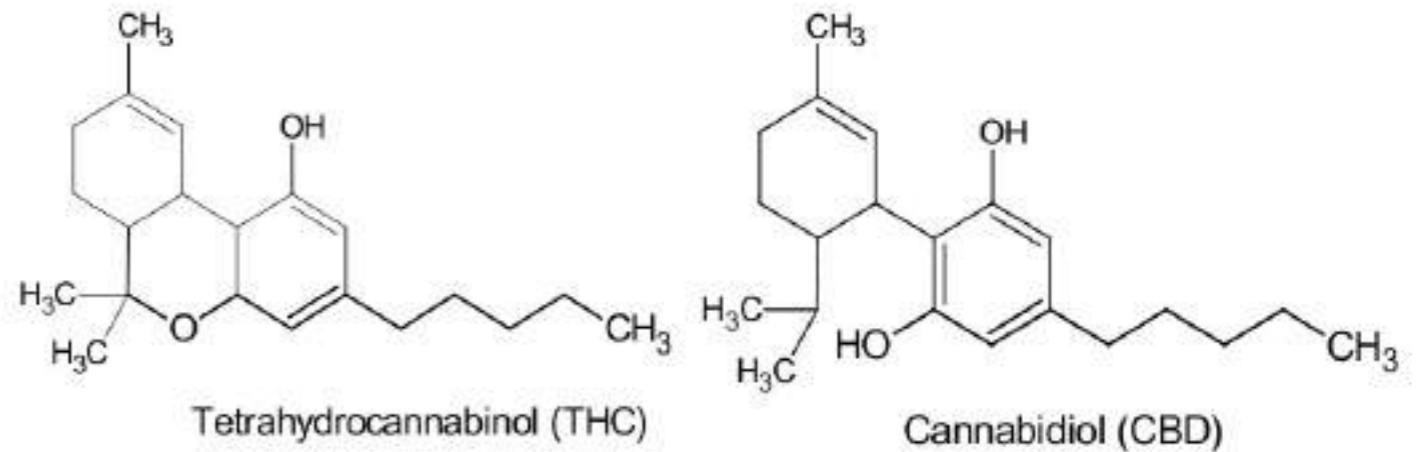
Cannabis Vs. Cannabinoids



- Over 100 botanically derived phytocannabinoids
Many directly impact the endocannabinoid receptor system
- Diverse pharmacology
- Hundreds of synthetic cannabinoids



THC vs CBD



- **THC drives most of the hallmark effects of cannabis (“high” feeling, increase in appetite, memory difficulties, etc.)**
- **Partial agonist at CB1 and CB2 receptor**
- **CBD does not produce the same “high” as THC, no abuse liability via oral route, but does produce drug effects**
- **Different and complex pharmacology**
- **CBD does NOT mitigate most effects of THC**
- **Several other cannabinoids that we know little about (CBG, CBC, CBN, THC analogues, terpenes)**

Why Has Cannabis Been Legalized?

- **Effective lobbying efforts**
- **Convincing medicinal case reports**
- **Increasing number of adults with past use and decreased perception of harm**

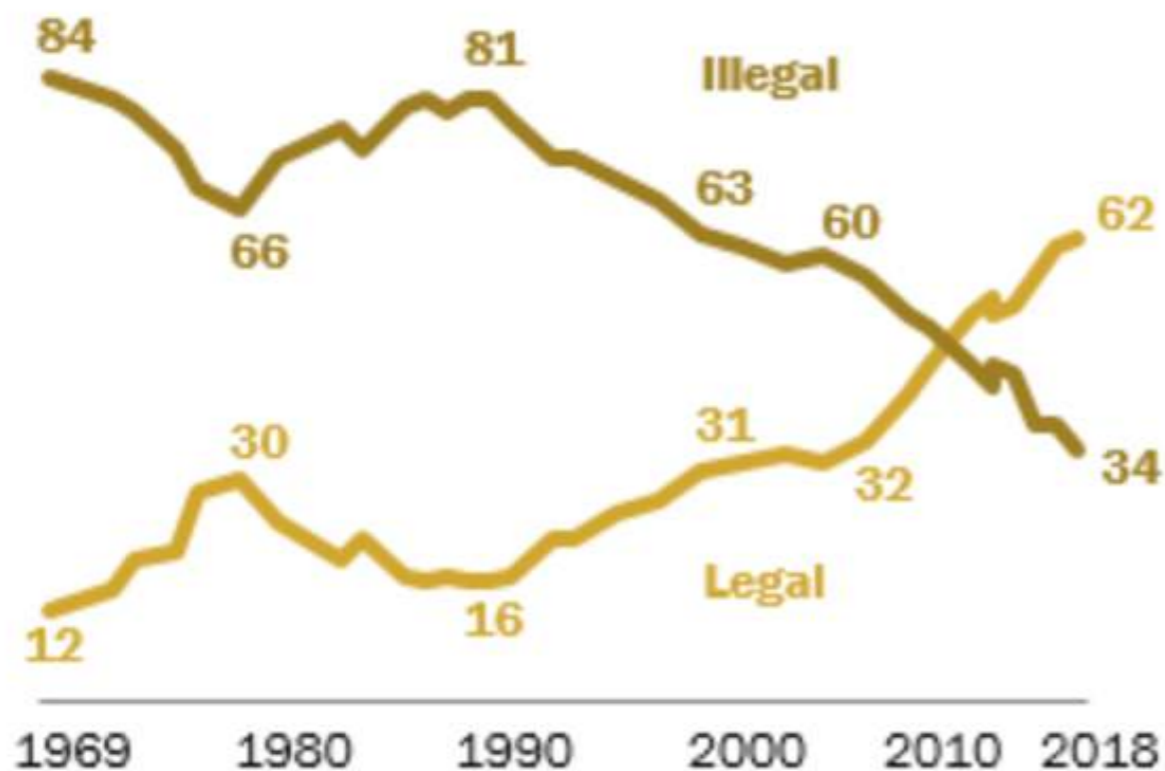


Legalization

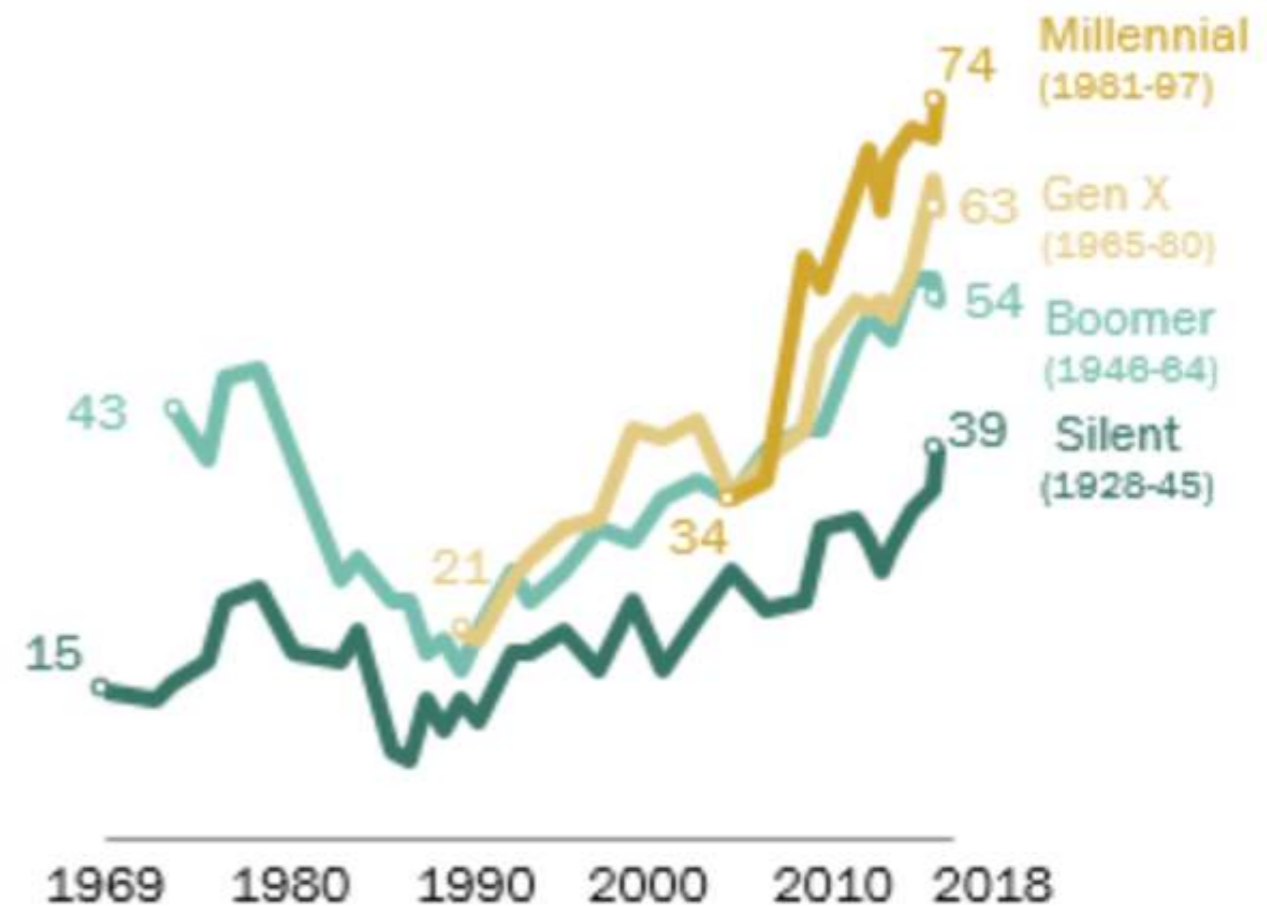


U.S. public opinion on legalizing marijuana, 1969-2018

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



% who say marijuana should be made legal



Note: Don't know responses not shown.

Source: Survey of U.S. adults conducted Sept. 18-24, 2018.

PEW RESEARCH CENTER

Impact of Legalization

- Substantial reduction in cost and stigma and increase in access
 - Roll-out of increasingly more palatable and more discreet products
 - Risk for accidental ingestion
 - Difficulty monitoring adolescent use
 - No change in alcohol use, mixed data on opioid use
 - Too early to fully assess public health impact
- 

Cannabis Use Metrics

Figure 13. Past Month Marijuana Use among People Aged 12 or Older, by Age Group: Percentages, 2002-2017

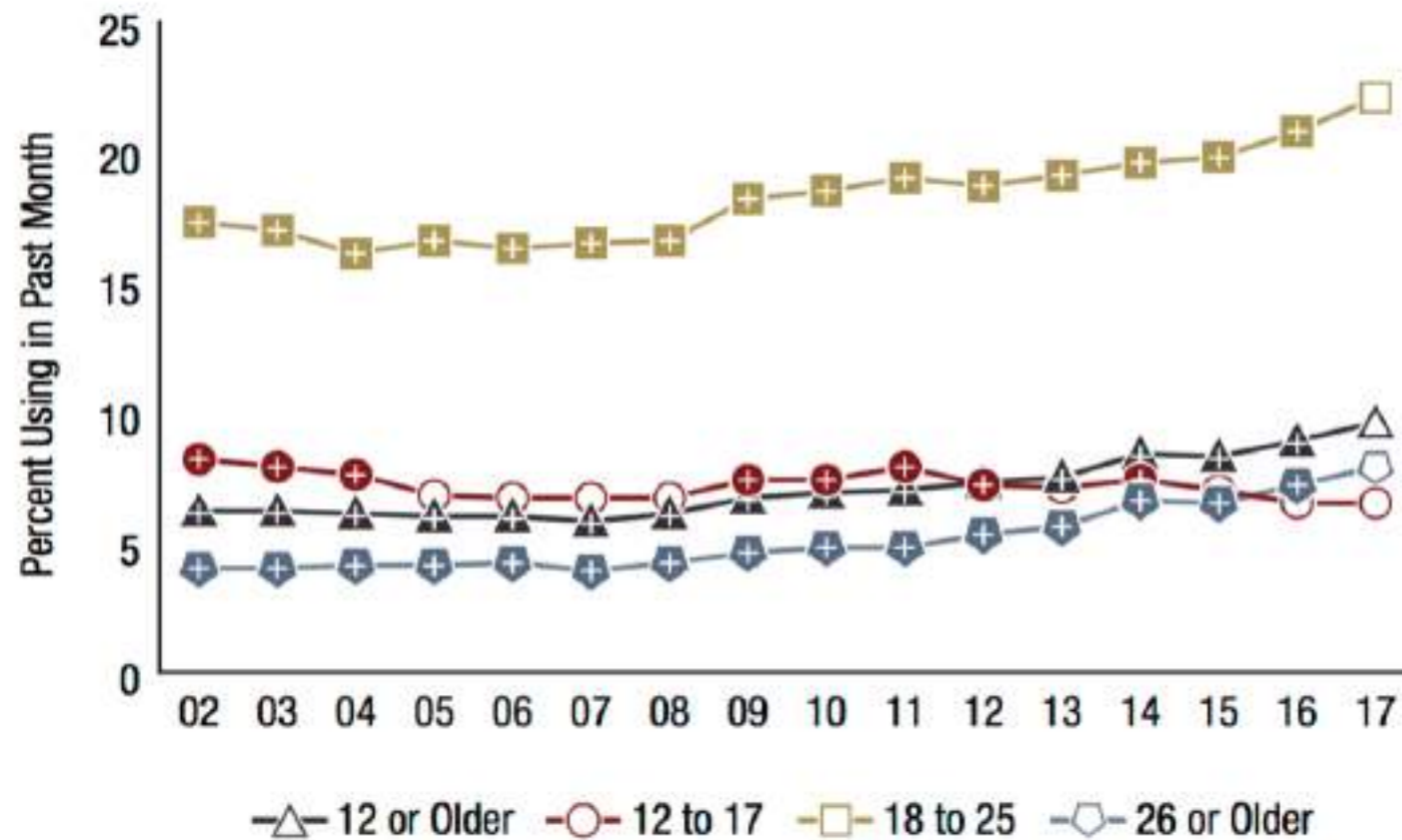
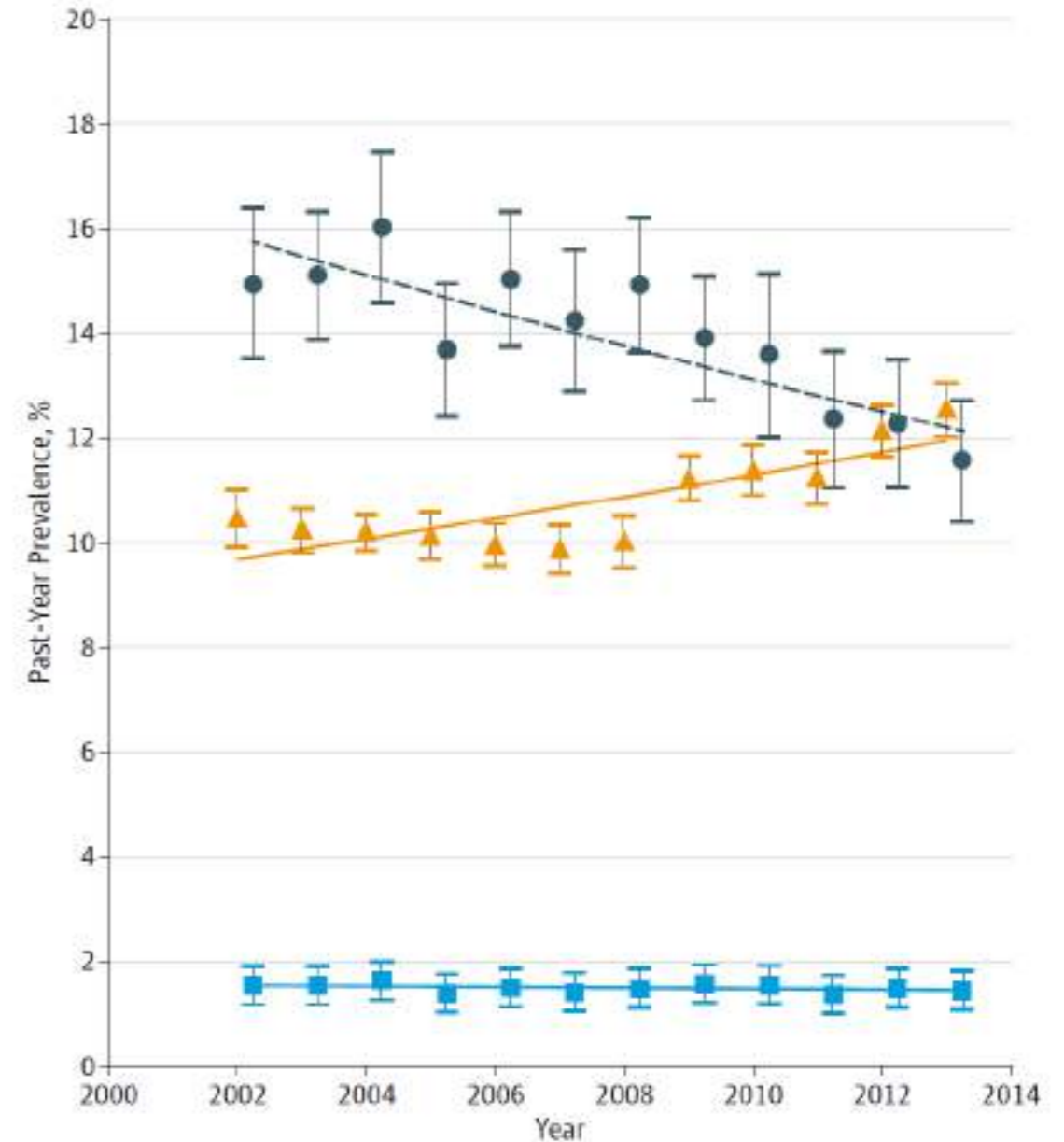


Figure. Past-Year Prevalence Estimates for Marijuana Use, Marijuana Use Disorder, and Marijuana Use Disorder Among Past-Year Users, 2002-2013



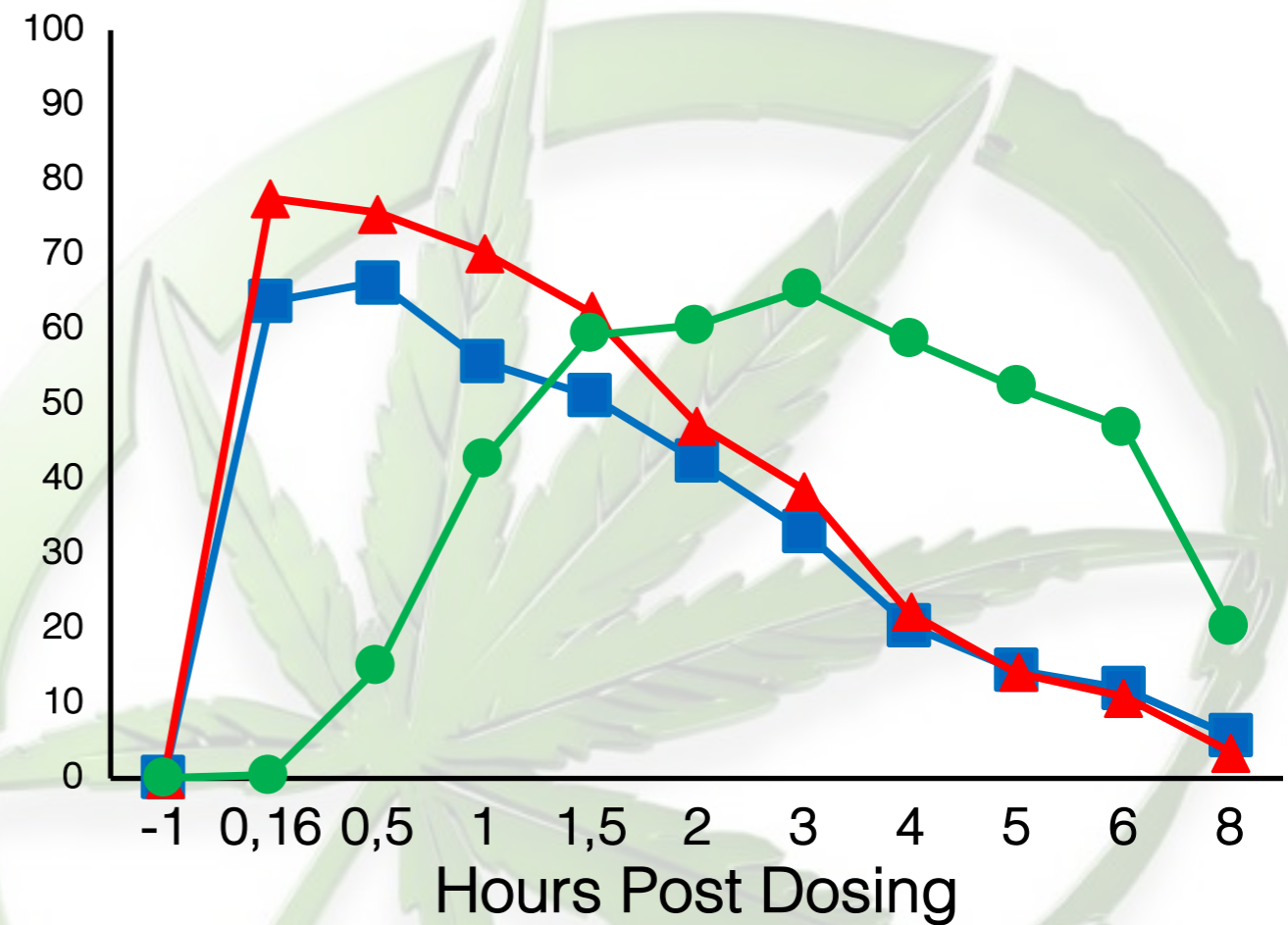
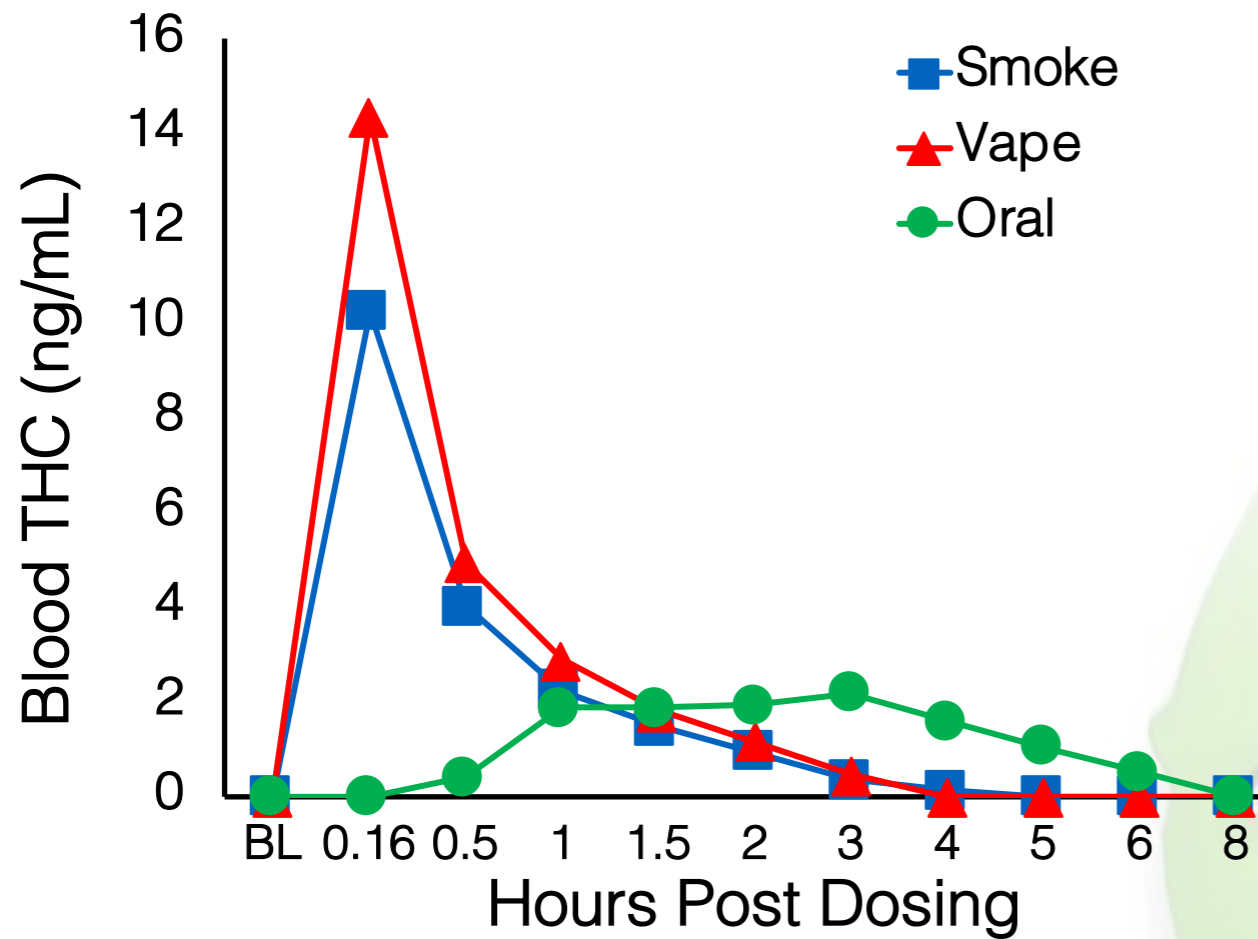
Lines represent fits to linear trend models and are not meant to describe the precise functional form of the trends. Triangles represent marijuana use; squares, marijuana use disorder; circles, marijuana use disorder among past-year users; and error bars represent 95% CIs.

Acute Effects of Cannabis



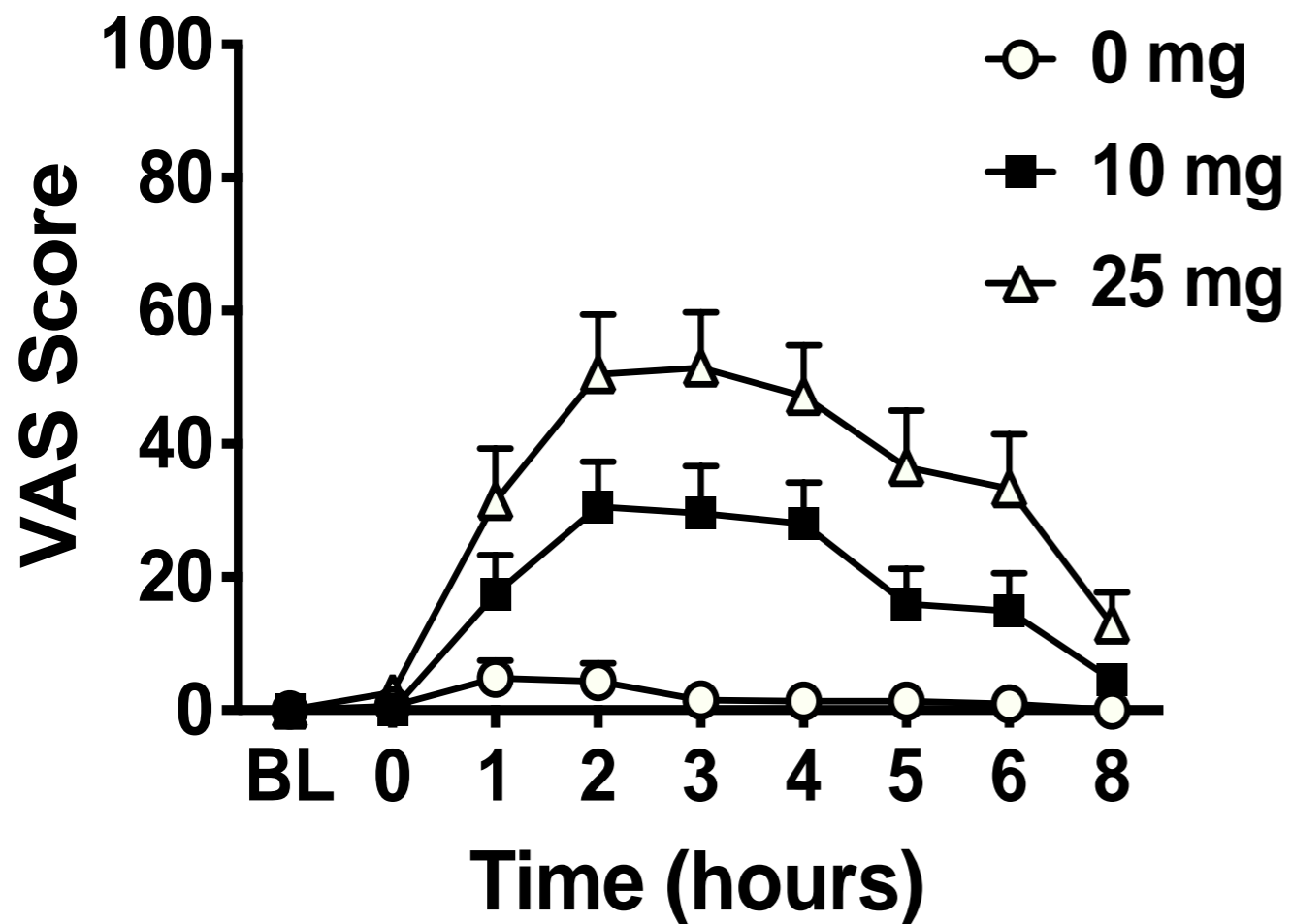
Impact of Route of Admin

25mg THC Dose

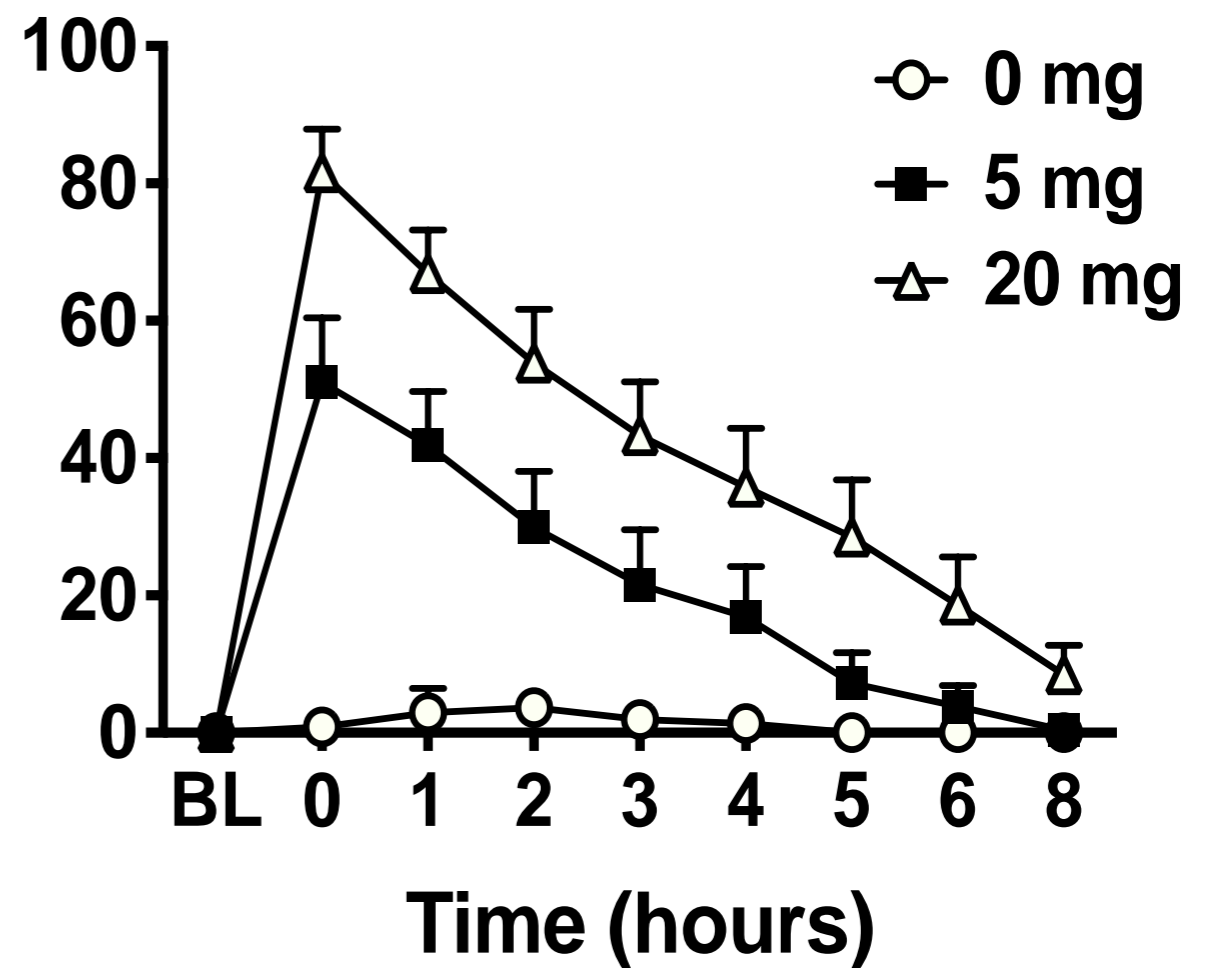


Impact of THC Dose on Subjective Drug Effects

Oral Cannabis

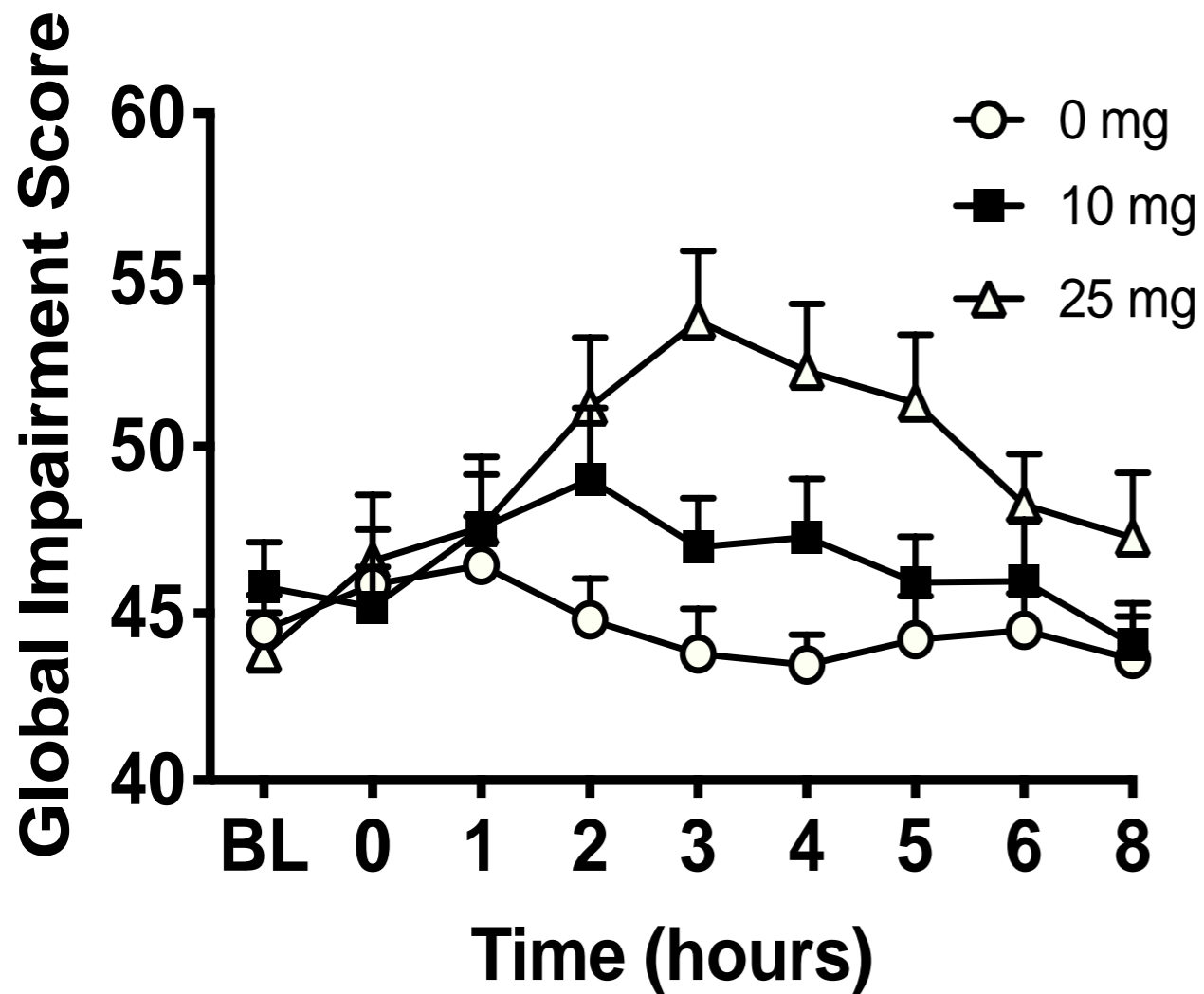


Vaped Cannabis

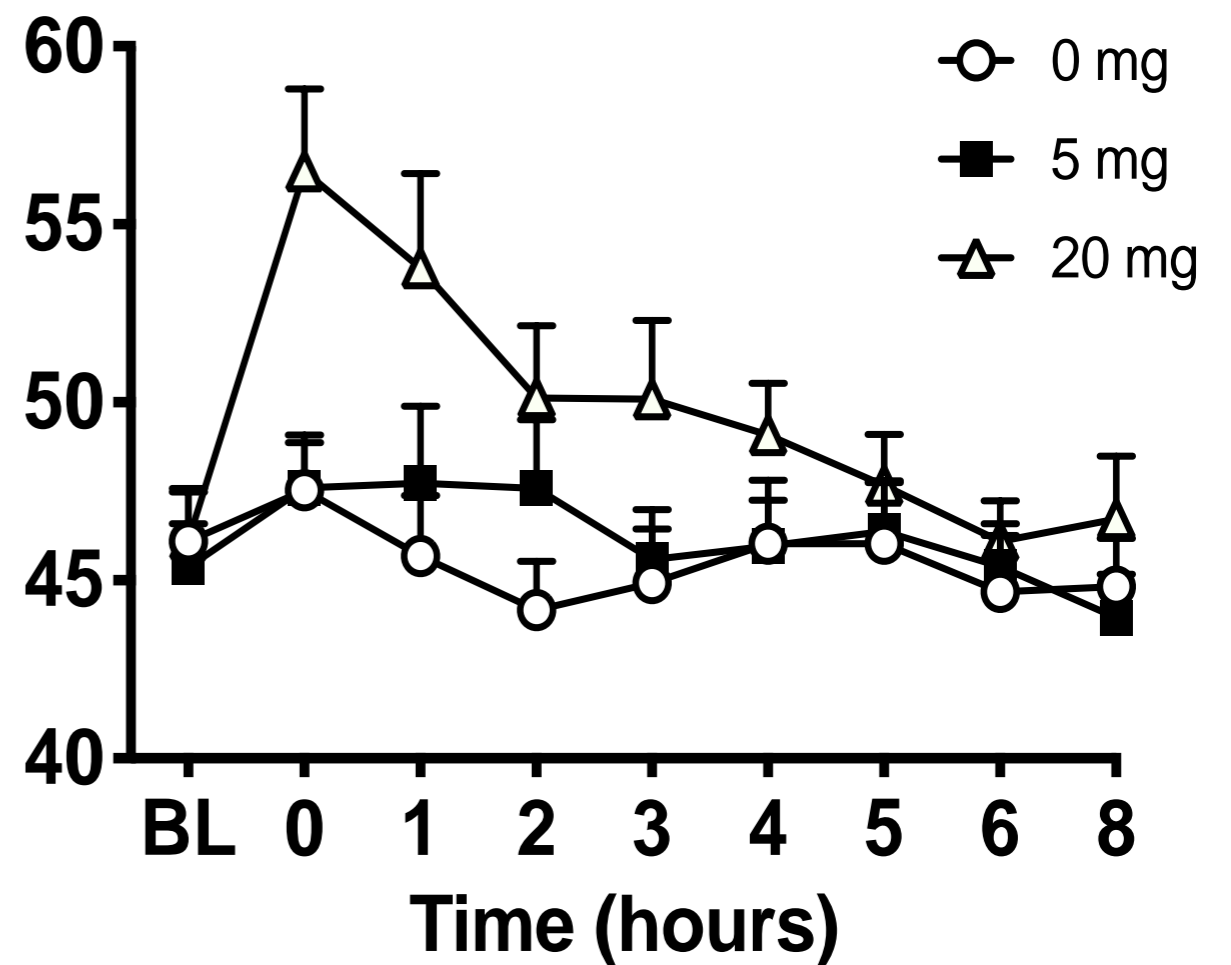


Impact of THC Dose on Cognitive Performance

Oral Cannabis



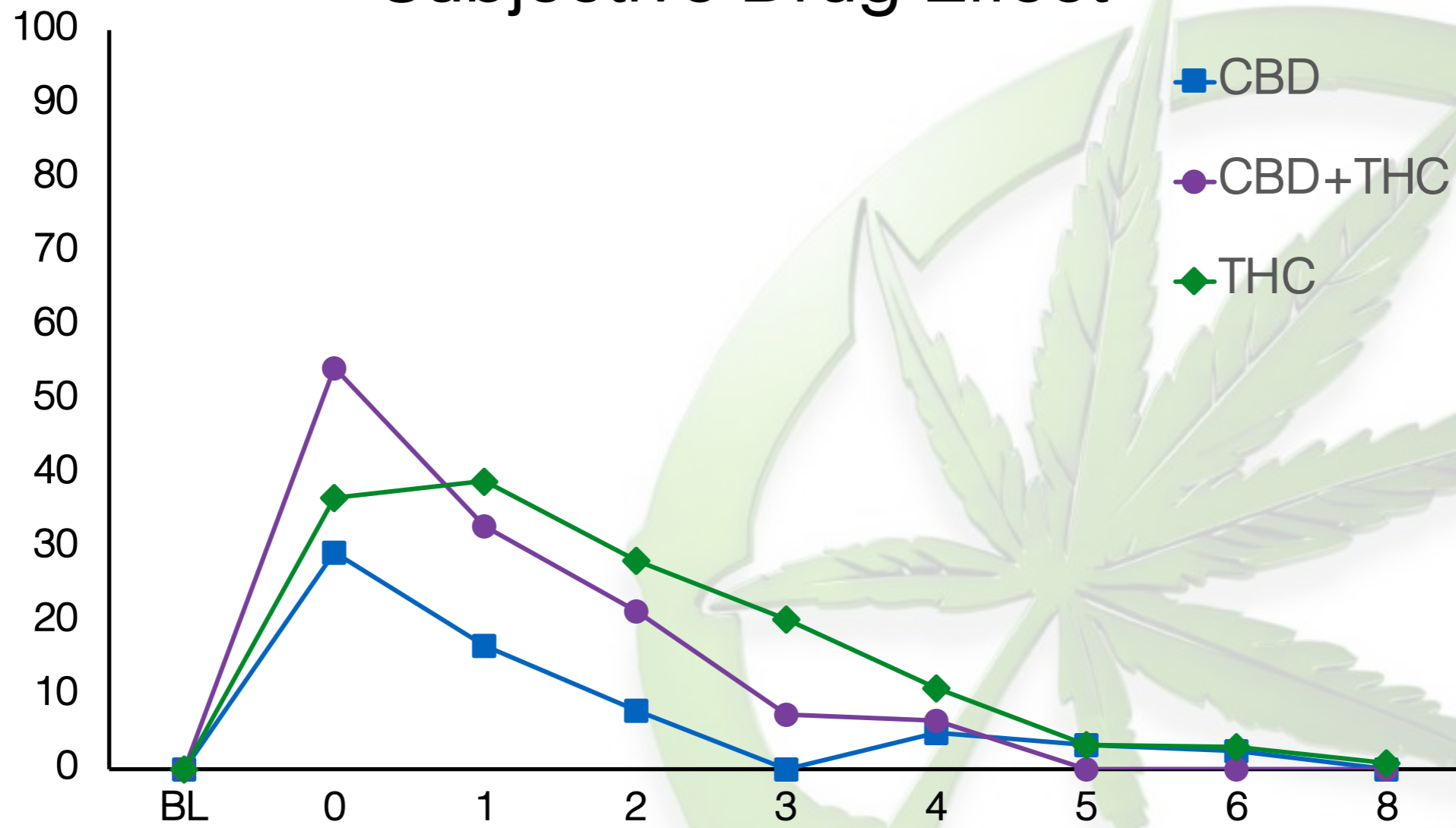
Vaped Cannabis



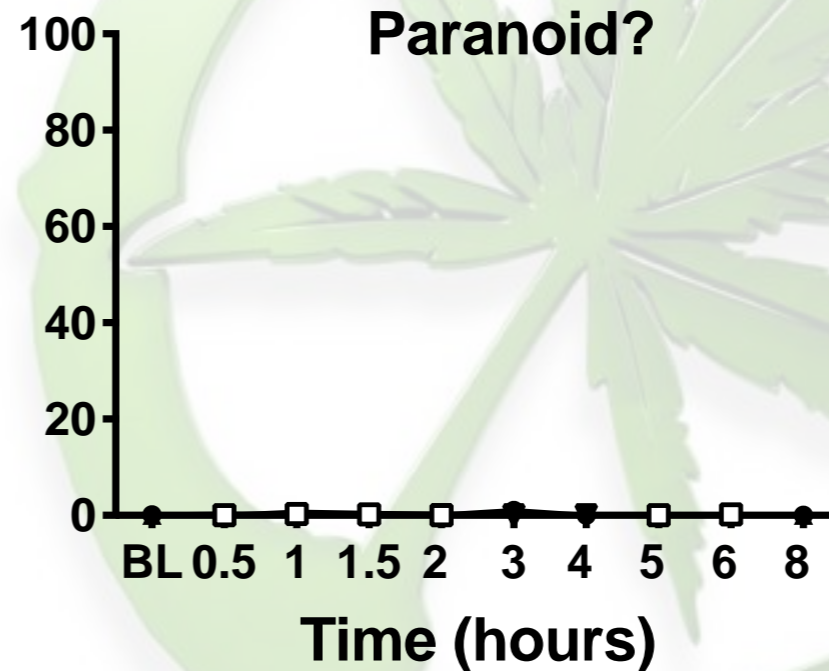
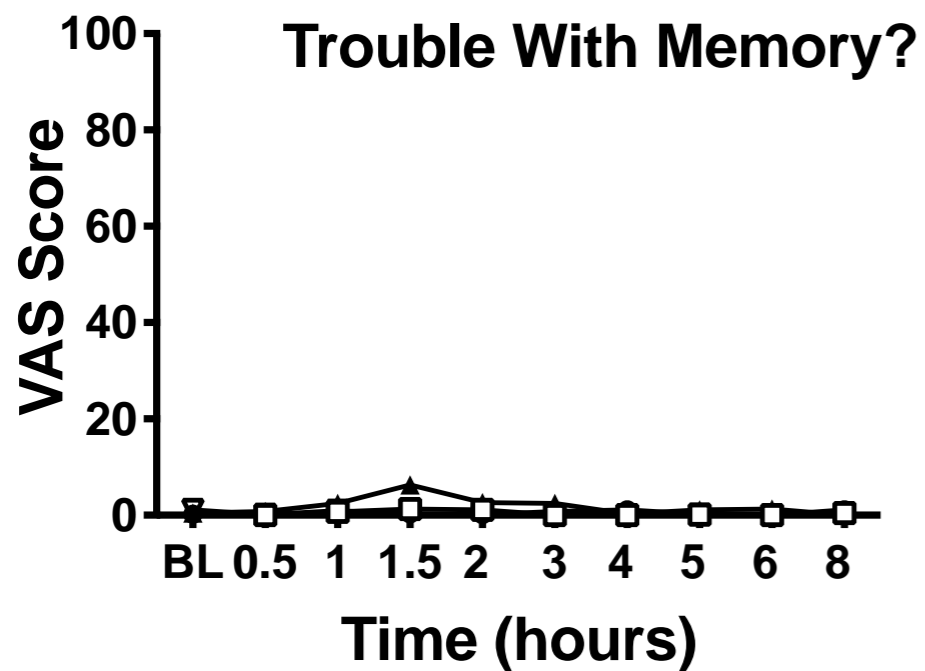
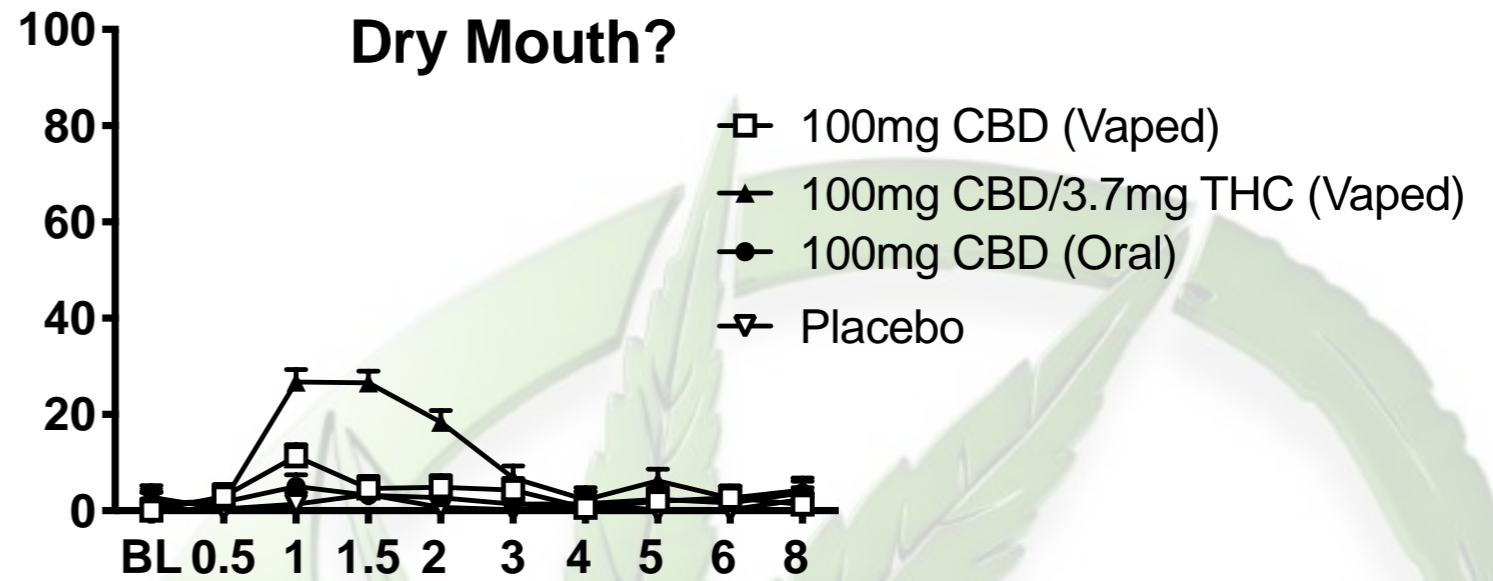
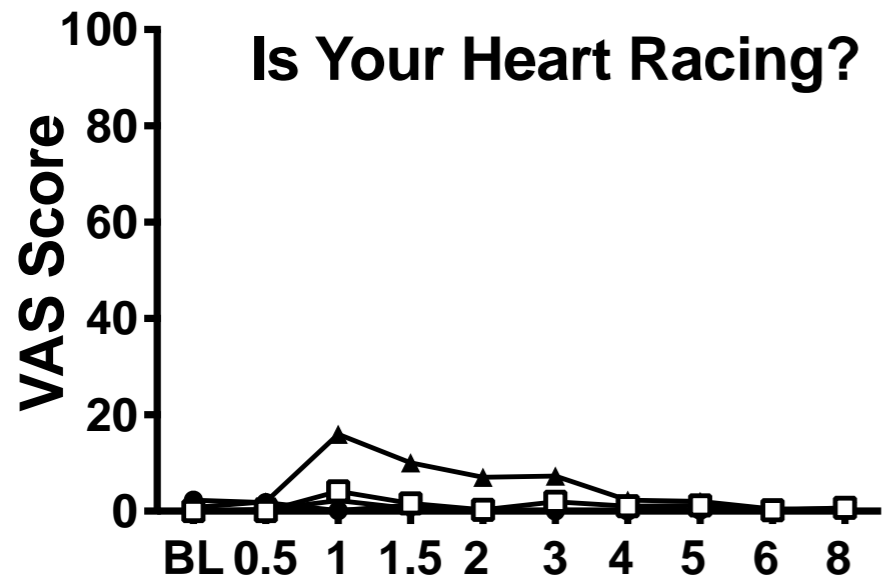
Impact of Chemotype

5mg THC Dose/100mg CBD

Subjective Drug Effect

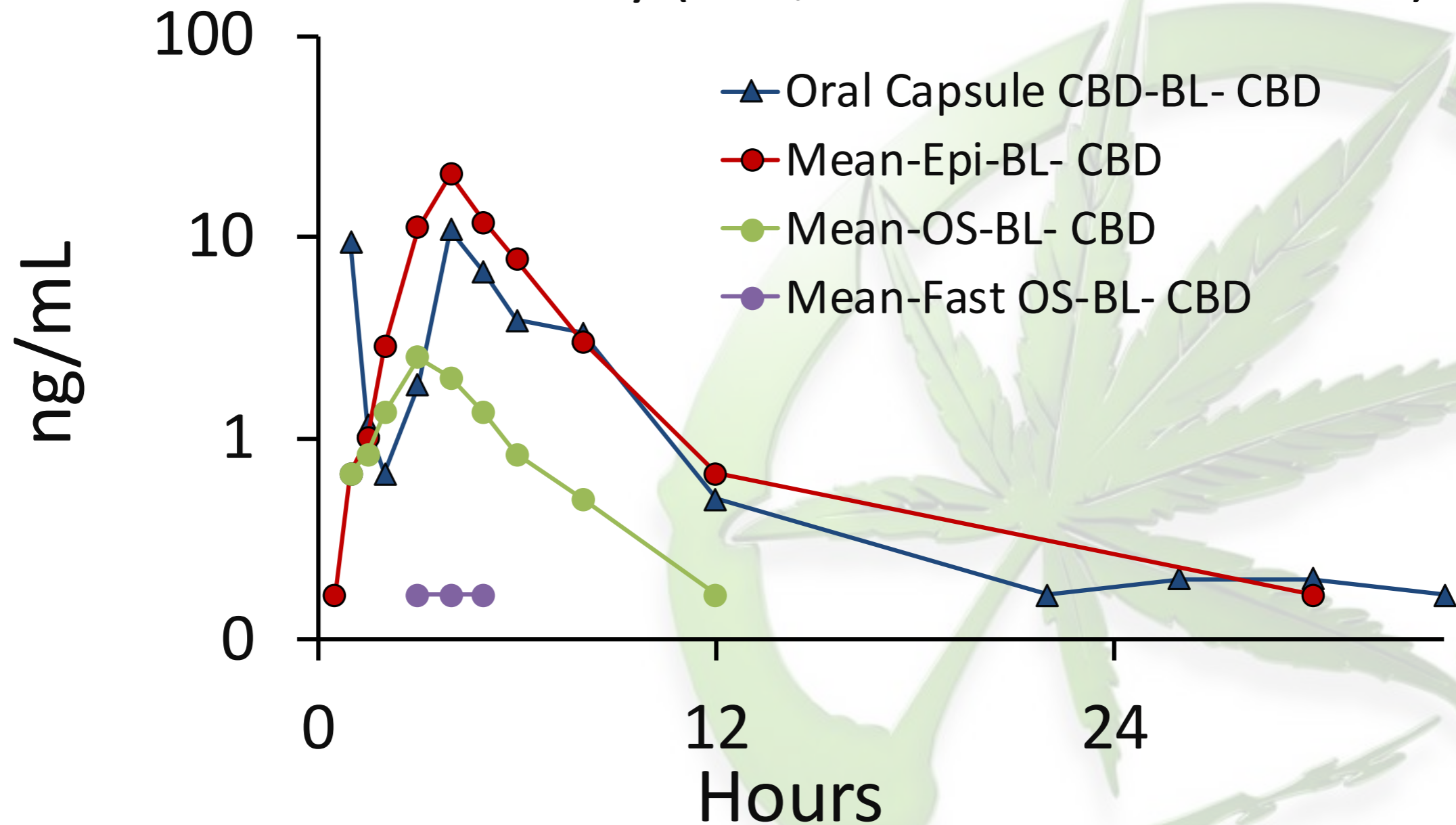


CBD Not THC-Like



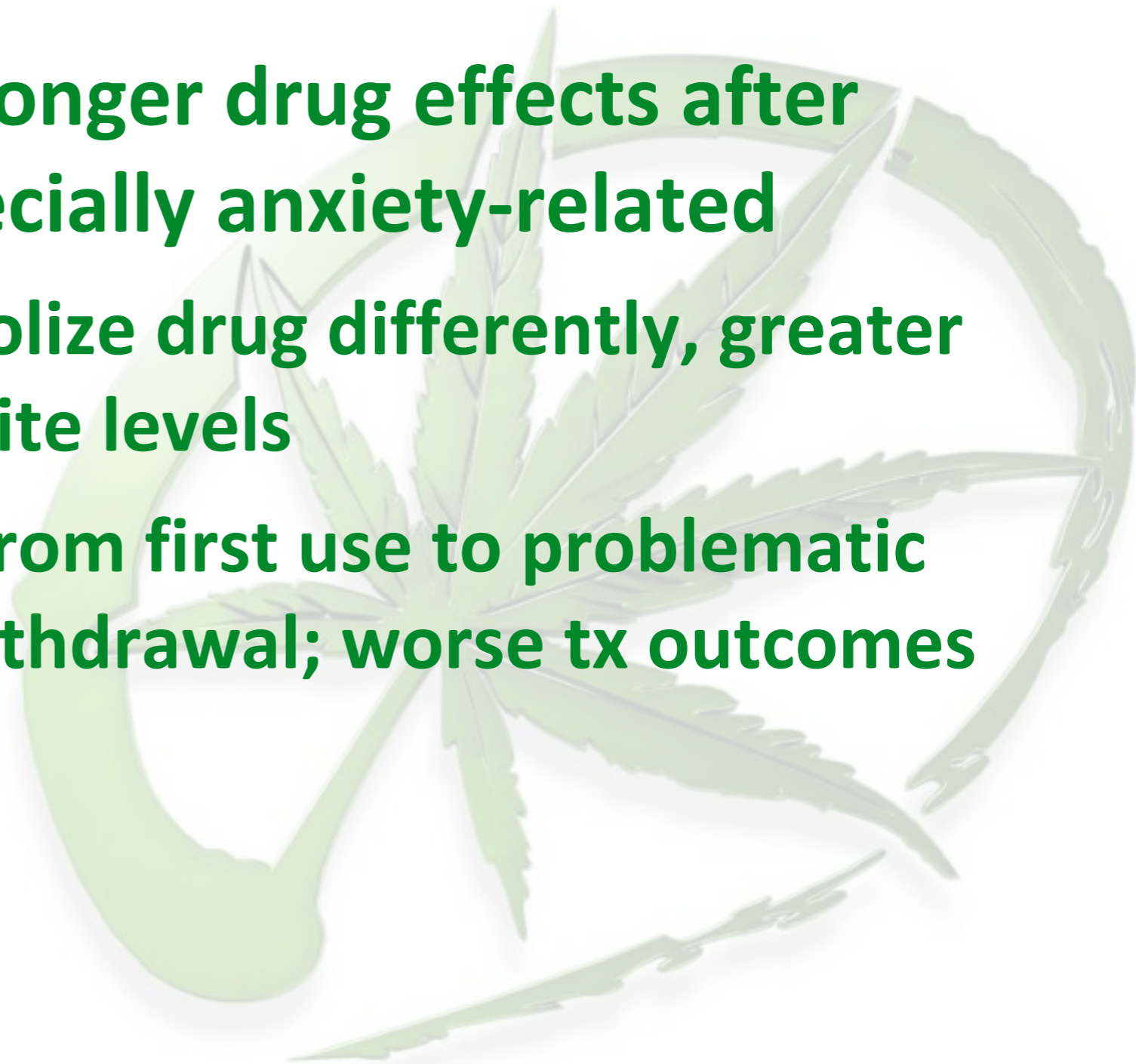
CBD in Blood by Formulation

CBD Study (n=6, Different Oral Routes)



Sex Differences

- **Neurobiology of cannabinoid system is different for men vs women**
- **Women report stronger drug effects after acute dosing, especially anxiety-related**
- **Women also metabolize drug differently, greater 11-OH-THC metabolite levels**
- **Faster progression from first use to problematic use; more severe withdrawal; worse tx outcomes**



Cure All or Snake Oil?

9 Major Health Benefits of Medical Marijuana



1 Treats Migraines
Cannabis has been very effective in the treatment of migraine headaches. Migraine headaches are vascular in source and are often preceded by an aura characterized by nausea, flashes of light, faintness or photophobia.

2 Slows Down Tumor Growth
Studies have shown that cannabis help to slow down the formation and slow down the production of cancer cells in body. It is also a natural anti-emetic, which makes it effective in preventing the nausea and vomiting related with chemo and radiation therapies. So taking marijuana slows down the tumor growth too.

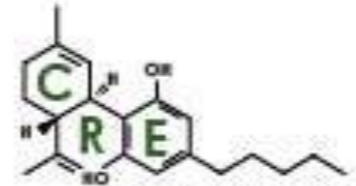
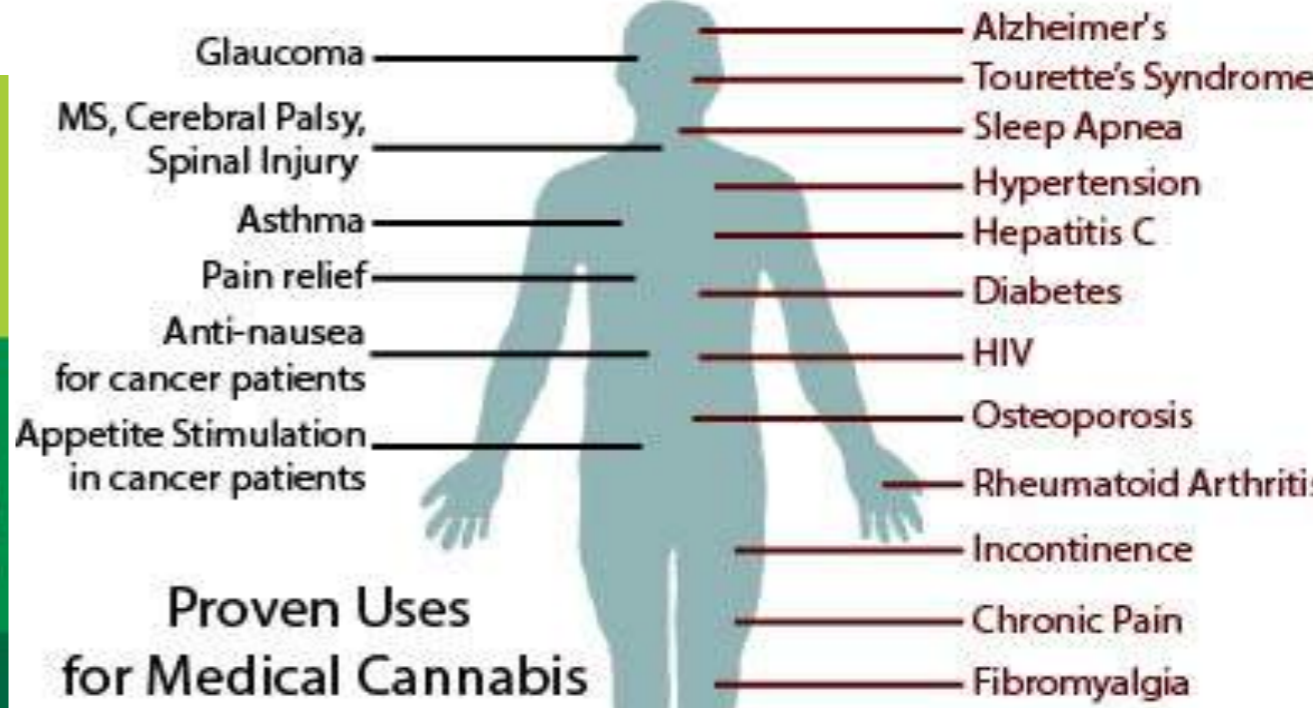
3 Relieves Symptoms of Chronic Diseases
Marijuana is one of the best natural pain relievers that can help sufferers of chronic pain live more relaxed lives. The side effects are often much less severe than the other common pain medications.

Prevents Alzheimer's

6 Prevents Seizures
Epilepsy is a kind of epilepsy which almost affects more than 2 million of Americans and 30 million of people worldwide. Epilepsy is a condition when some of the brain cells become abnormally excitable. People using marijuana to control epilepsy should be alert when there is any removal of any tablets which control epilepsy may leave you more susceptible to the seizure. Marijuana is an anticonvulsant. People with epilepsy are advised to consult a doctor when using and THC because there is not enough sufficient knowledge about the interaction of any medicinal properties of the drug and seizure.

7 For ADD and ADHD
Many people who struggle with ADD and ADHD find that medical cannabis provides them focus to study and their level of mental well-being is high. There are no clinical studies on this but there are some anecdotal reports have shown an increase that people who take marijuana daily and regularly with the use of cannabis can be better mechanism dependent.

8 Relieve PMS
Millions of women have an issue on Premenstrual Syndrome (PMS) that involves the symptoms of moodiness, irritability, fatigue, bloating and hair shedding. Many women report that they have had several different medications but none of them are effective to treat the medical issues. Cannabis can be a help to ease your symptoms and take care of the unpleasant symptoms of PMS.



Emerging Uses for Medical Cannabis

DO YOU SUFFER FROM ANY OF THESE CONDITIONS?

- ANXIETY
- CHRONIC PAIN
- ARTHRITIS
- FIBROMYALGIA
- GLAUCOMA
- INSOMNIA
- DEPRESSION
- CANCER
- HIV/AIDS
- NAUSEA
- MUSCLE SPASMS
- CROHN'S DISEASE
- EPILEPSY
- SEIZURES
- STRESS
- ANOREXIA
- ADD/ADHD
- MIGRAINES
- PMS
- NEUROPATHY
- & MANY MORE

MARIJUANA

MAY BE AN EFFECTIVE TREATMENT.



Clinical Research Required

Proper drug development includes study of:

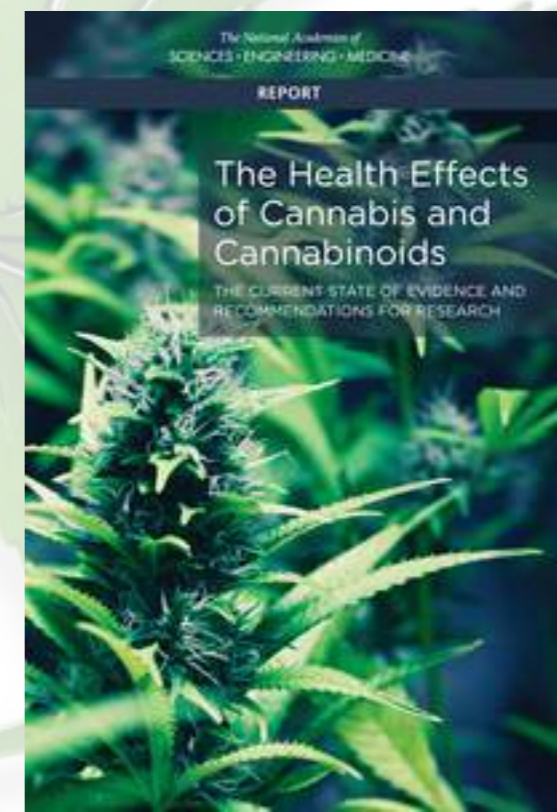
- Pharmacokinetics/Bioavailability
- Safety
- Initial efficacy (placebo controlled)
- Comparative efficacy
- Post-marketing surveillance

Product and health condition
clearly defined



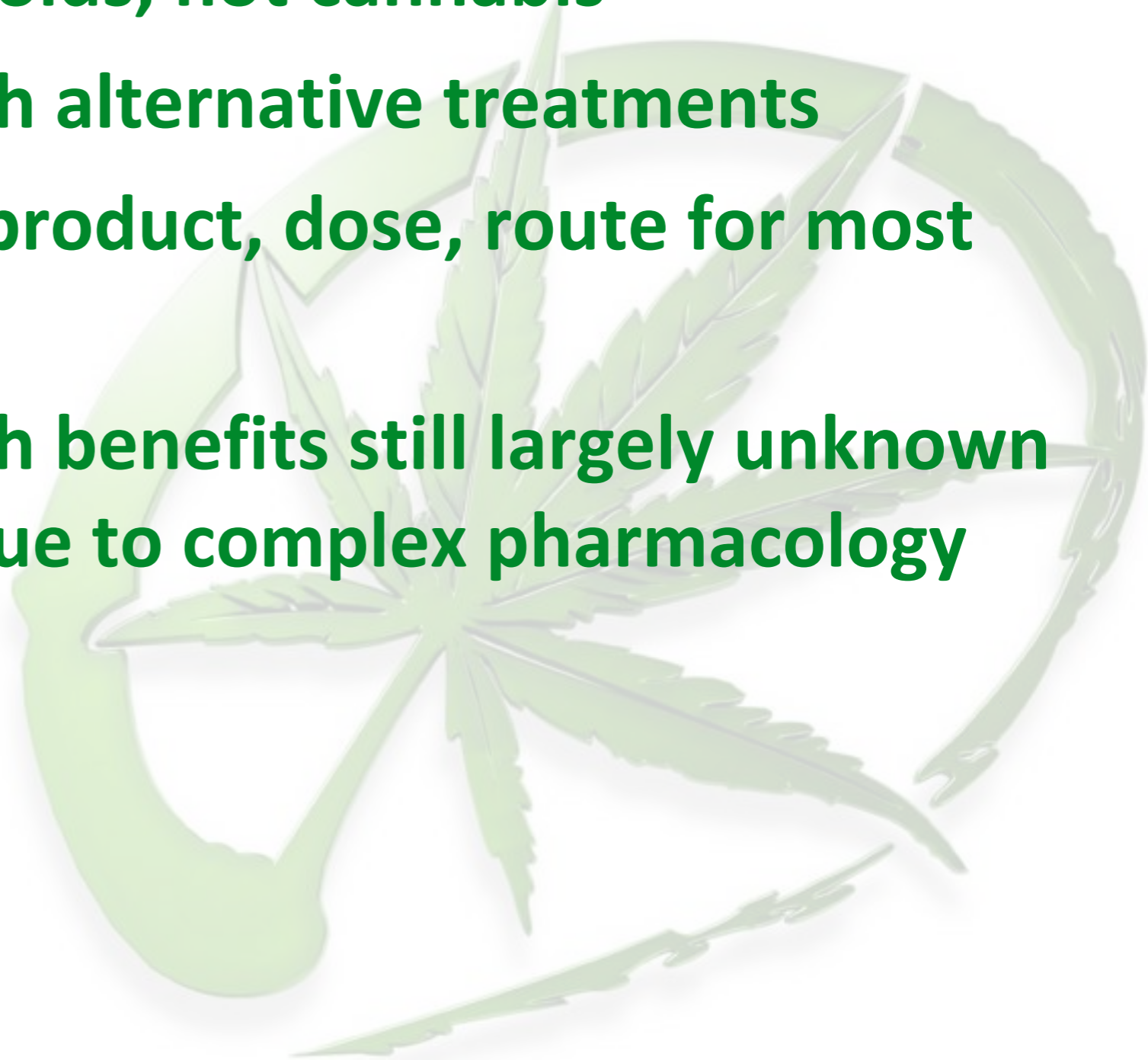
National Academies Report 2017

- Found conclusive/substantial evidence to support clinical use for chronic pain, MS, and nausea or emesis due to chemotherapy
- Moderate evidence was found to support short-term use for sleep dysfunction
- Ineffective for dementia, glaucoma, depression associated with pain or MS
- After report, Epidiolex approved for rare seizure disorders



Limitations of Cannabis Data

- **Relatively small studies completed**
- **Most with cannabinoids, not cannabis**
- **No comparisons with alternative treatments**
- **Still lacking info on product, dose, route for most health conditions**
- **Mechanism of health benefits still largely unknown especially for CBD due to complex pharmacology**



Observational Research

- Opportunity to compare health of cannabis users vs. non-users
- Look for trends in product use, dose, outcomes by health condition
- Evaluate changes over time

Realm of Caring Observational
Research Registry

www.theroc.us/orr



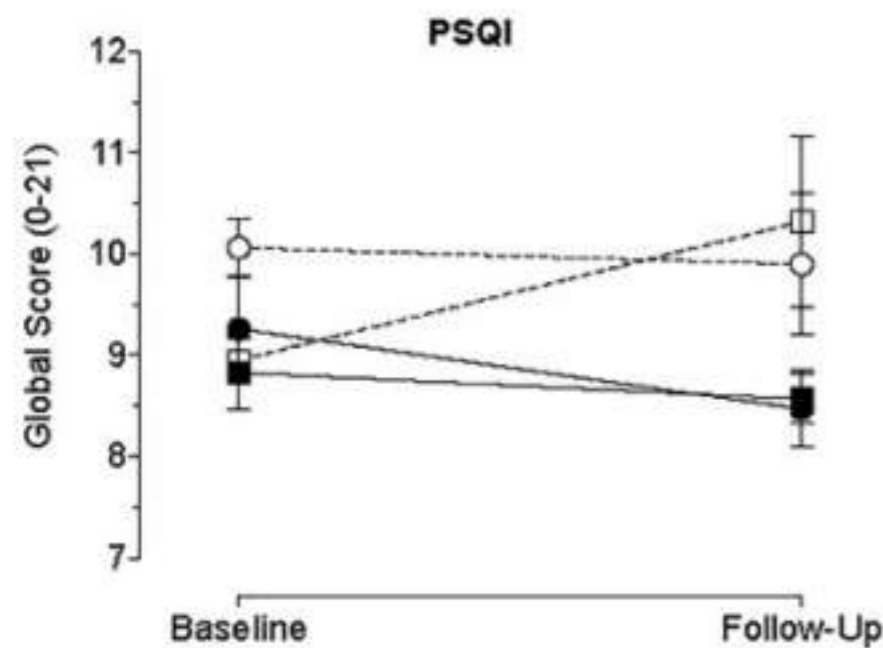
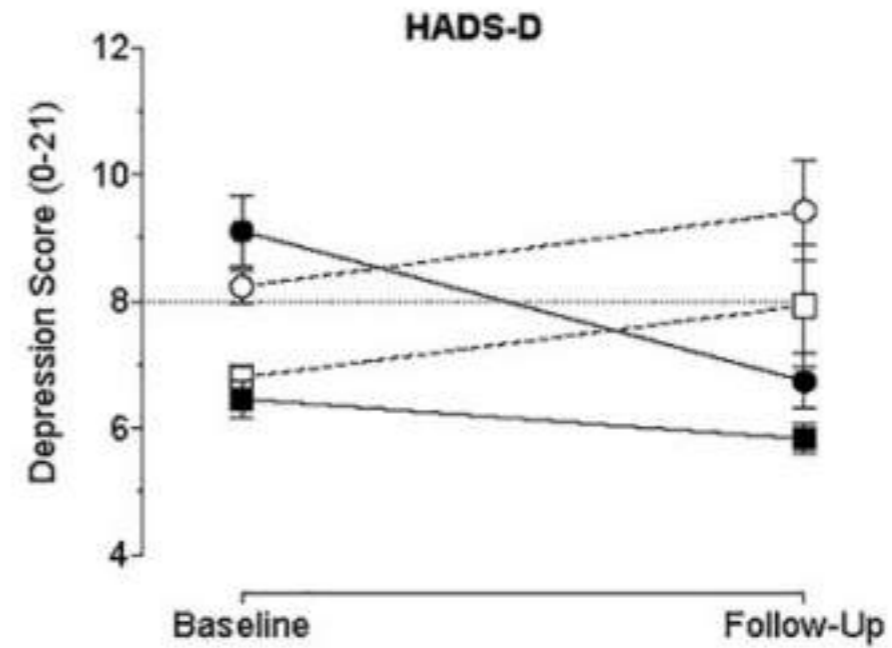
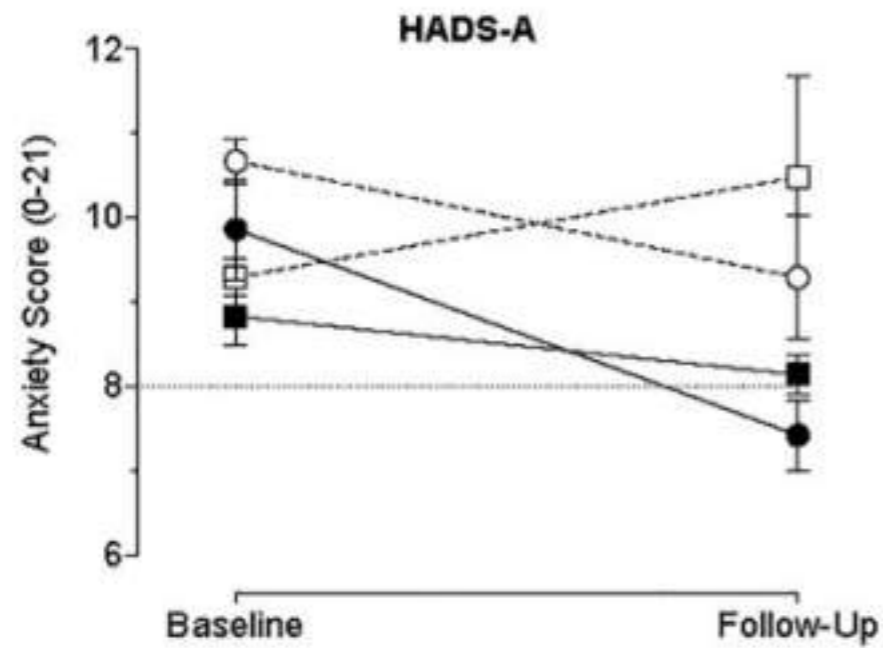
Patient Outcome Comparison

	Cannabinoid Users	Non-Users	p-Value
WHOQOL-BREF			
Quality of Life Rating	3.5 (1.2)	3.2 (1.2)	<.001
Health Satisfaction	2.4 (1.1)	2.1 (1.0)	<.001
Physical Health	12.1 (3.8)	11.2 (3.6)	<.001
Psychological Health	13.3 (3.3)	12.2 (3.3)	<.001
Social Health	13.3 (4.0)	12.5 (4.3)	<.01
Environmental Health	15.0 (3.2)	14.8 (3.0)	.18
NPRS (Pain)	3.9 (2.9)	4.3 (3.0)	<.01
CSHQ (Child Sleep)	30.2 (10.4)	34.0 (11.9)	<.01
PSQI (Adult Sleep)	8.9 (4.0)	9.7 (4.0)	<.01
HADS			
Anxiety Subscale	9.2 (5.2)	10.5 (5.1)	<.001
Depression Subscale	6.7 (4.8)	8.4 (5.1)	<.001

Patient Outcome Comparison

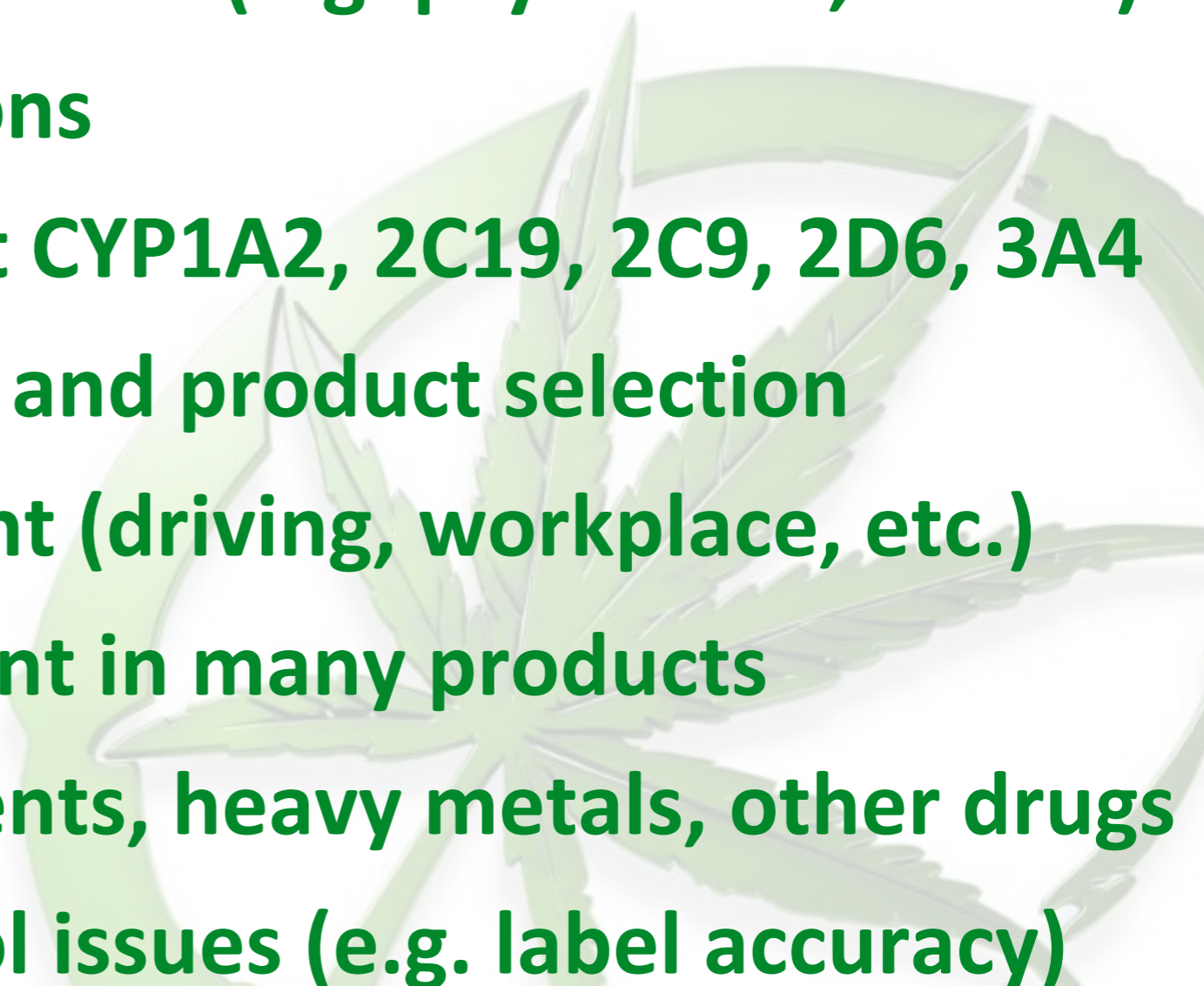
Dependent Variable, (N) Predictor	Exp(B)	95% CI	Likelihood Ratio
Prescription Medications, (N=774) Group (Cannabinoid Users)	- 0.86*	- 0.77, 0.96	7.71** -
OTC Medications, (N=763) Group (Cannabinoid Users)	- 1.06	- 0.93, 1.22	0.74 -
Outpatient Visits, (N=731) Group (Cannabinoid Users)	- 1.03	- 0.89, 1.19	0.11 -
Emergency Room Visits, (N=307) Group (Cannabinoid Users)	- 0.61**	- 0.44, 0.84	9.31** -
Hospital Admissions, (N=180) Group (Cannabinoid Users)	- 0.54*	- 0.34, 0.87	6.35* -
Sick Days, (N=675) Group (Cannabinoid Users)	- 0.83	- 0.63, 1.09	1.86 -

Within-Subject Changes

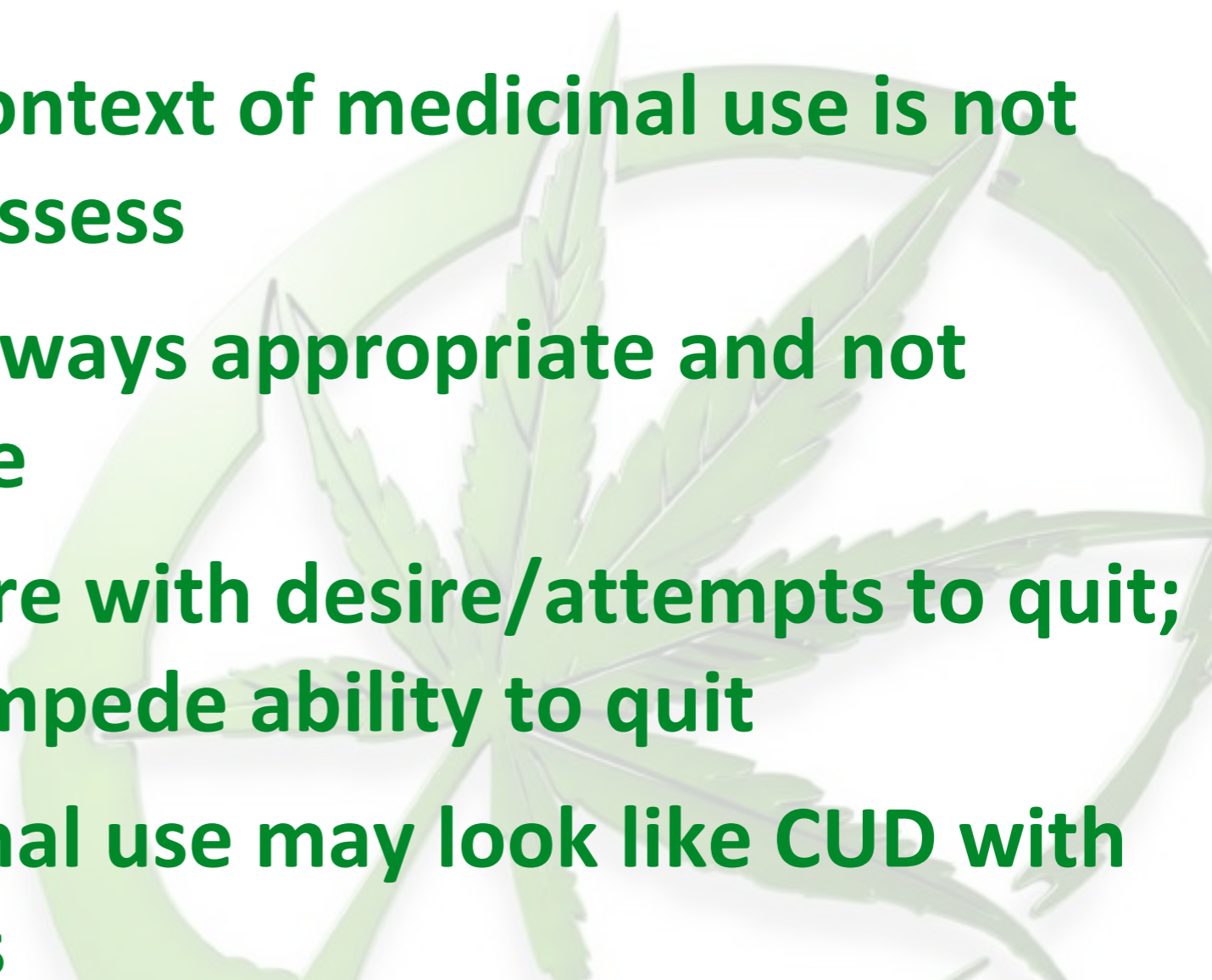


- Control Initiate
- Cannabis Continue
- Control No Initiate
- Cannabis Discontinue

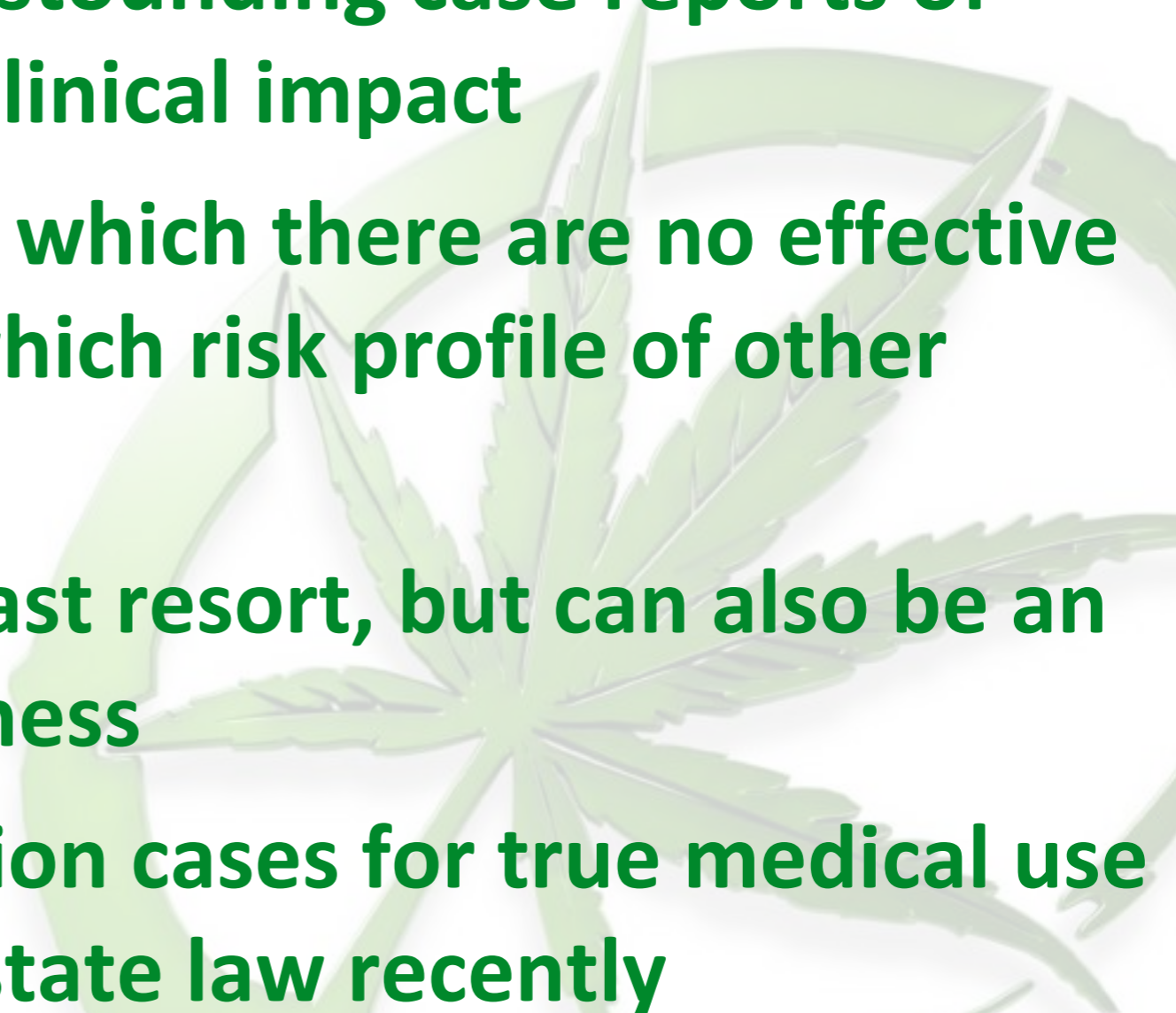
Major Risks of Medicinal Cannabidiol

- **Adverse events: high THC doses, females, high risk sub-groups comorbidities (e.g. psychiatric, cardio)**
 - **Drug-drug interactions**
 - **CBD may impact CYP1A2, 2C19, 2C9, 2D6, 3A4**
 - **Guidance for dosing and product selection**
 - **Cognitive impairment (driving, workplace, etc.)**
 - **Contaminants present in many products**
 - **Pesticides, solvents, heavy metals, other drugs**
 - **Other quality control issues (e.g. label accuracy)**
- 


Cannabis Use Disorder (CUD)

- CUD is very real, well defined, and clinically significant
 - Risk of CUD in the context of medicinal use is not known, difficult to assess
 - Medicinal use not always appropriate and not exclusive of risky use
 - Legality may interfere with desire/attempts to quit; medical need may impede ability to quit
 - Appropriate medicinal use may look like CUD with current assessments
- 

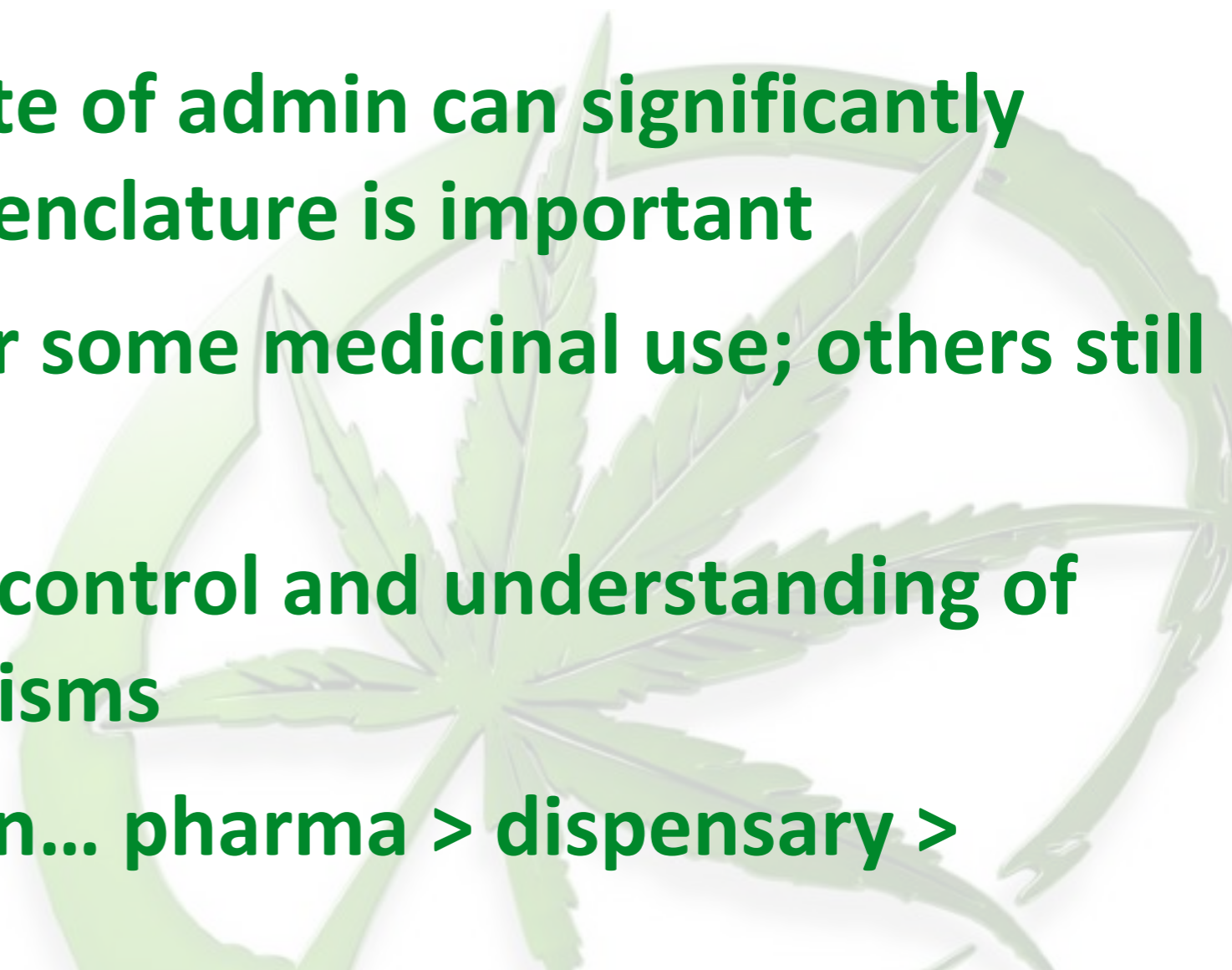
Reasons to Consider Medicinal Cannabis Use

- Many examples of astounding case reports of significant positive clinical impact
 - Health conditions in which there are no effective treatments, or for which risk profile of other treatment is poor
 - Typically tried as a last resort, but can also be an adjunct in severe illness
 - No federal prosecution cases for true medical use in accordance with state law recently
- 

Recommendations

- Evaluate as any other novel therapeutic
 - Learn more cannabis/cannabinoids
 - Engage in open conversations with patients about risk/benefit of use
 - Know your institutional policy
 - Try FDA approved medications first; if patient goes to dispensary make explicit product recommendations before they go (route and chemotype)
 - Meet/evaluate state-legal businesses
 - Conduct research and disseminate case reports
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Summary

- Cannabis is chemically complex and has tremendous potential for both health benefit and harm
 - Chemotype and route of admin can significantly impact effects; nomenclature is important
 - Sufficient science for some medicinal use; others still pending good data
 - Need better quality control and understanding of therapeutic mechanisms
 - Proceed with caution... pharma > dispensary > web/street
- 

Thanks!!

rvandrey@jhmi.edu

