Using Human Laboratory Methods to Understand the Pharmacokinetics and Pharmacodynamics of Oral Cannabinoid Products

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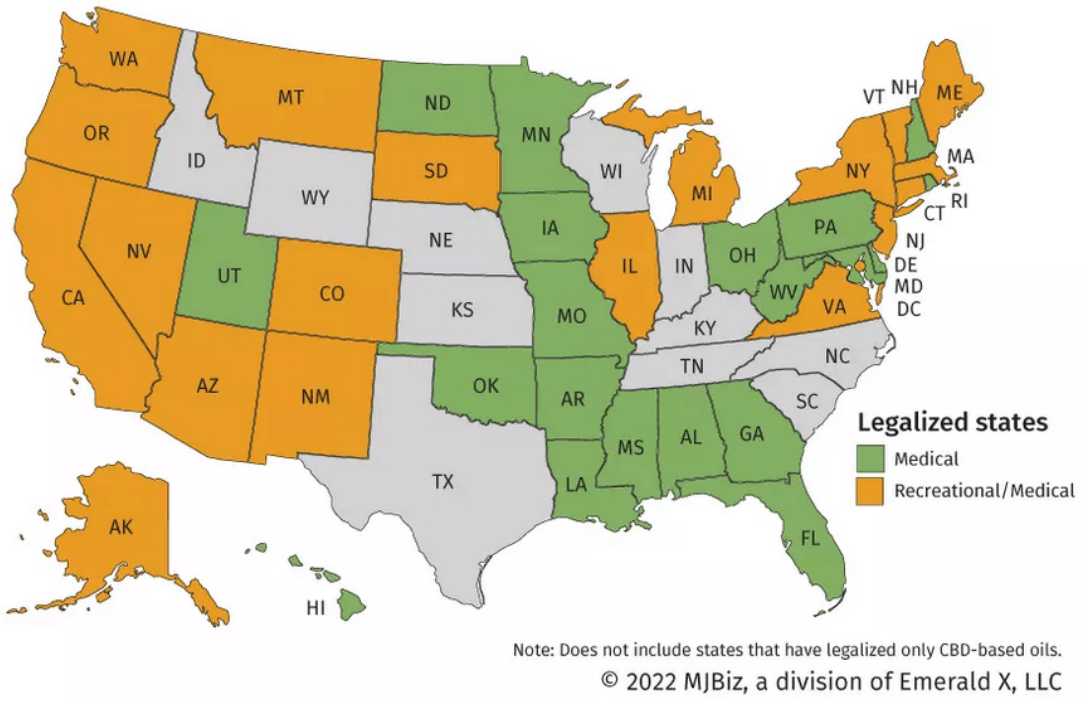
Disclosure Information

Tory Spindle, PhD.

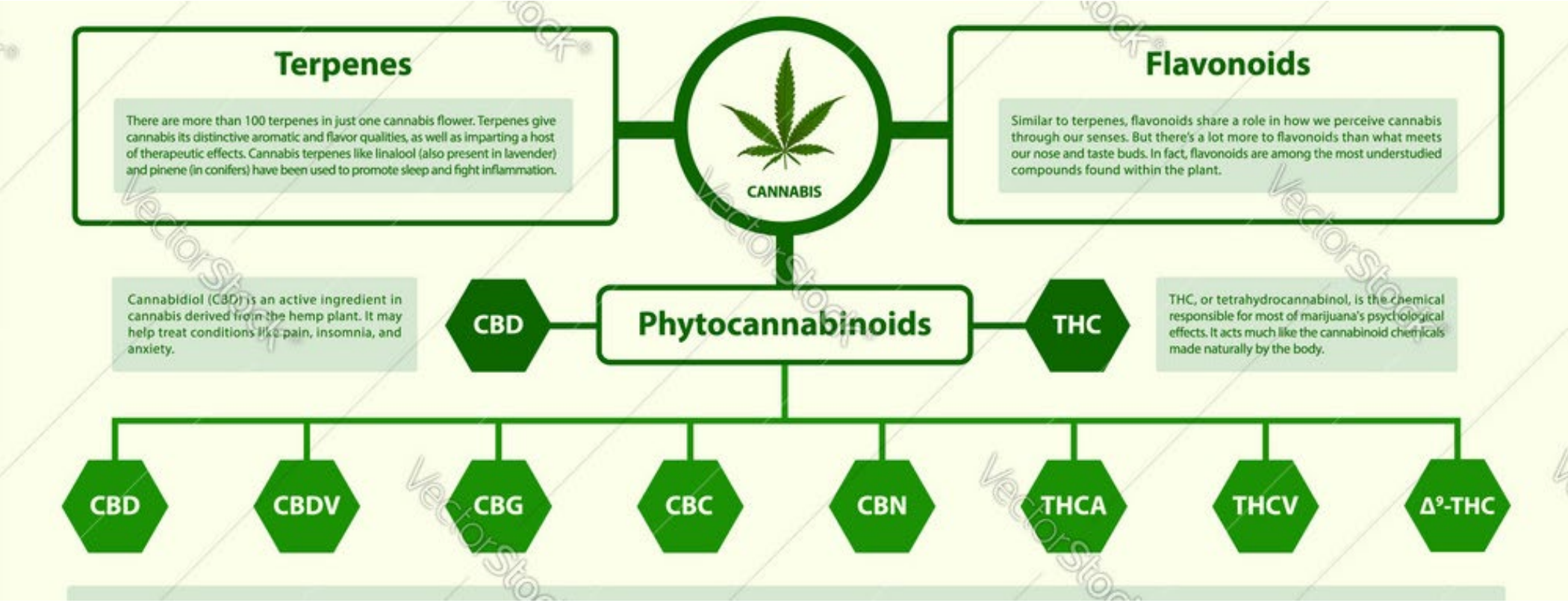
- Dr. Spindle has served as a consultant to Canopy Growth Inc
- The research being presented today is not related to this consulting work

Cannabis Laws are Changing



- 38 U.S. states + Washington D.C. allow medicinal and 19 states (+ D.C.) allow non-medicinal “recreational” cannabis use
- Cannabis is still considered illegal at the federal level
- Cannabis with ≤0.3% THC (*aka* Hemp) and anything derived from it EXCEPT THC is legal

Cannabis Contains Many Compounds



Many Forms of Cannabis + Routes of Administration

Many Different Oral Cannabis Products or “Edibles”

Various food matrices and liquid vehicles for edibles.

Background on Cannabis Edibles

- Edibles are now the second most popular form of cannabis (next to smoked flower)
- Approximately 1/3rd of cannabis users have tried edibles
- Users report that the duration and intensity of edibles' effects are highly unpredictable (possibly due to product diversity, inaccurate labeling, difficulty with dose titration)
- Responsible for the majority of ER visits related to over-intoxication from cannabis

Questions About Cannabis Edibles

- How do cannabis edible effects differ from smoking or vaping cannabis? Are the effects weaker/stronger at a given THC dose? Does the time-course of effects differ?
- What product features or user factors may influence the acute effects of edibles?
- Do edibles have drug-drug interactions with other medications?
- Do edibles impair driving performance? Can impairment be detected in individuals who recently used them?

Systematic Studies Needed

- Clinical Laboratory Research
- Johns Hopkins University Behavioral Pharmacology Research Unit (BPRU)

Clinical Laboratory Methods

Biological samples

- Measure THC + metabolites and other cannabinoids in blood, oral fluid, and urine

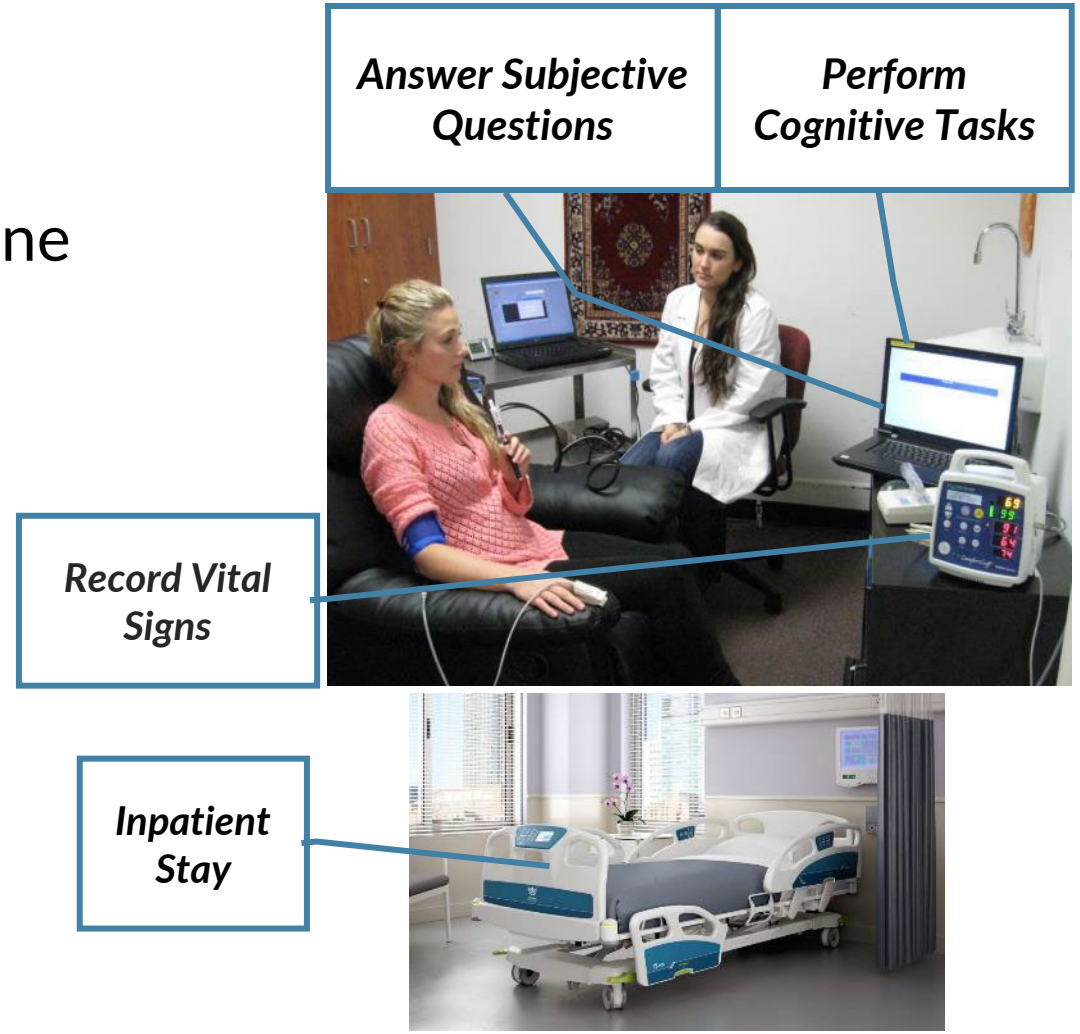
Subjective effects

- Positive effects (abuse liability)
- Negative effects (adverse events)

Cognitive performance testing

- Working memory
- Psychomotor functioning
- Divided Attention

Vital Signs (Heart rate, blood pressure)



Clinical Laboratory Methods (cont.)

Simulated Driving Performance

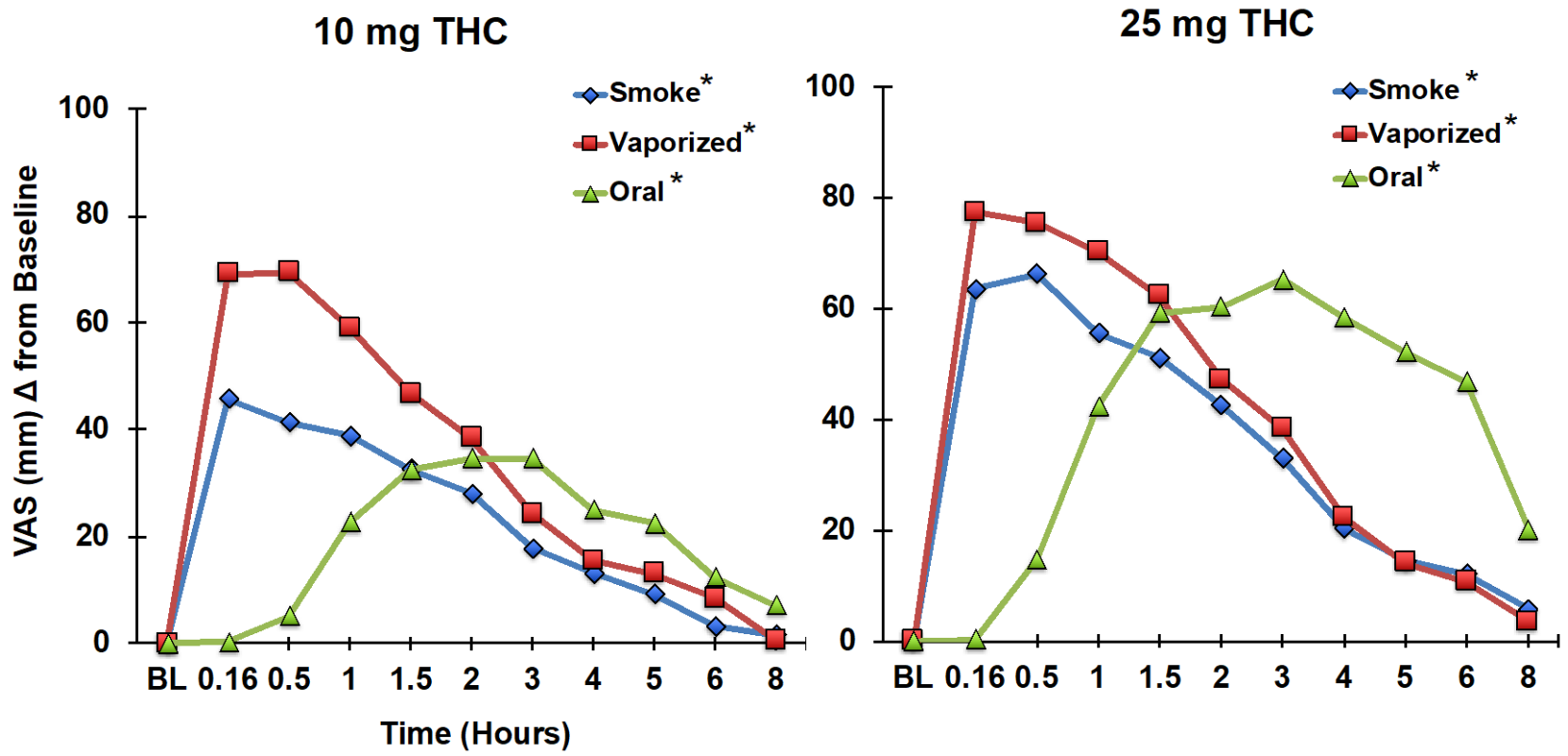
Overview

- PK/PD differences between edibles and other routes of administration (smoking, vaping)
- Interactive effects of THC + CBD
- Drug-drug interactions between edibles and common prescription or OTC medications
- Influence of product formulation and diet
- Measuring impairment from cannabis edibles

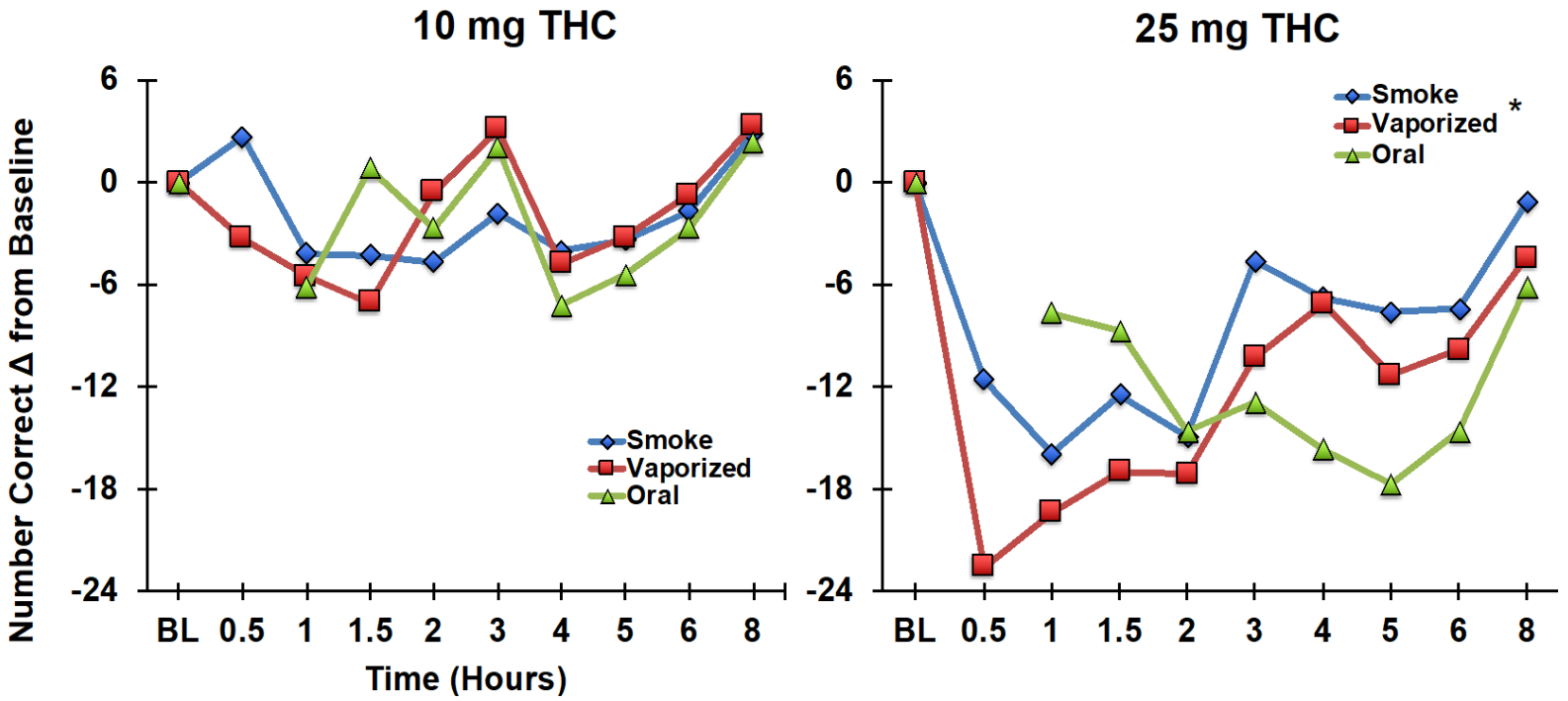
Route of Administration Studies – Smoked vs. Vaporized vs. Oral Cannabis

- Controlled cannabis dosing studies
  - Oral cannabis dosing studies – cannabis-infused brownies (0, 10, 25, 50 mg THC)
  - Smoked and vaporized study (0, 10, 25 mg THC)
- Subjective, cognitive, cardiovascular, and pharmacokinetic (i.e., urine, blood, oral fluid) assessments in each
- Similar protocol – assessments timepoints mirrored across studies
- Each focused on infrequent cannabis users who had no recent cannabis exposure

Subjective Ratings of “Feel Drug Effect”



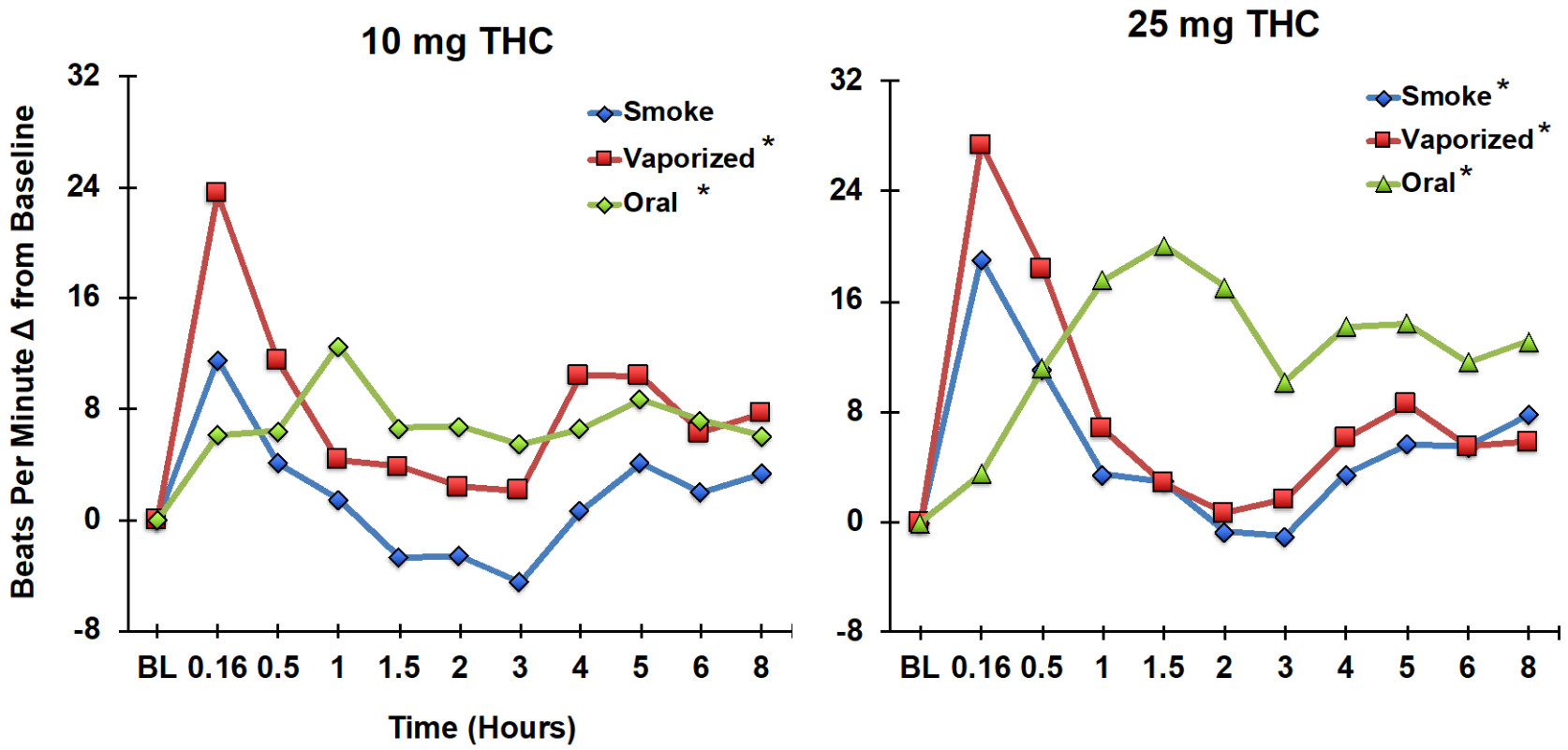
Cognitive Performance –PASAT



2

2	3	4	5	6	7	8	9	10

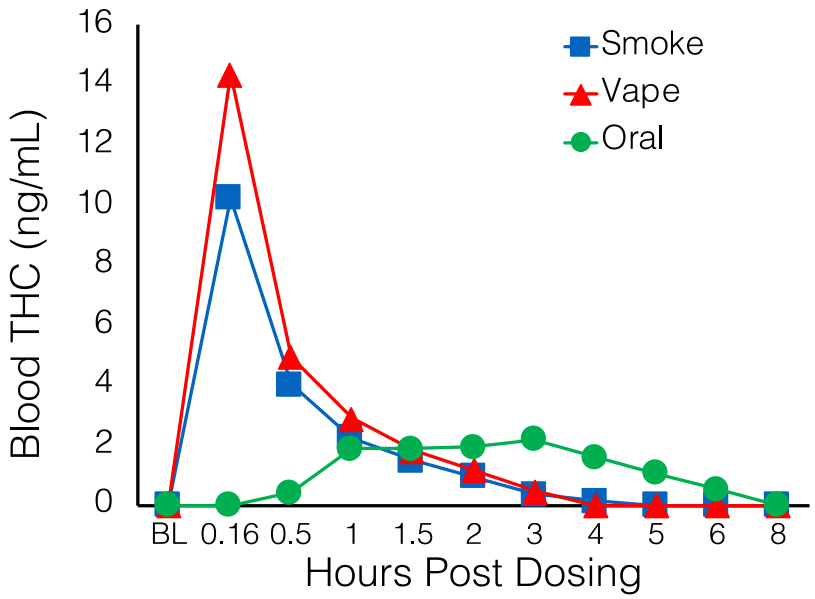
Heart Rate (beats per min)



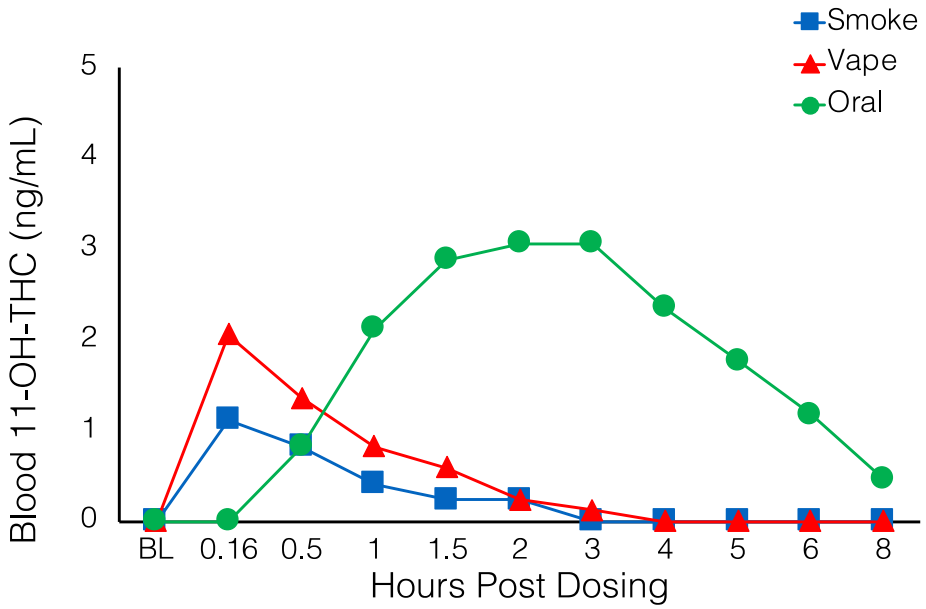
Data from: Schlienz et al., 2020, Drug and Alcohol Dependence Spindle et al., 2018, JAMA Network Open

Blood THC and 11-OH-THC – 25 mg Dose

Whole Blood THC

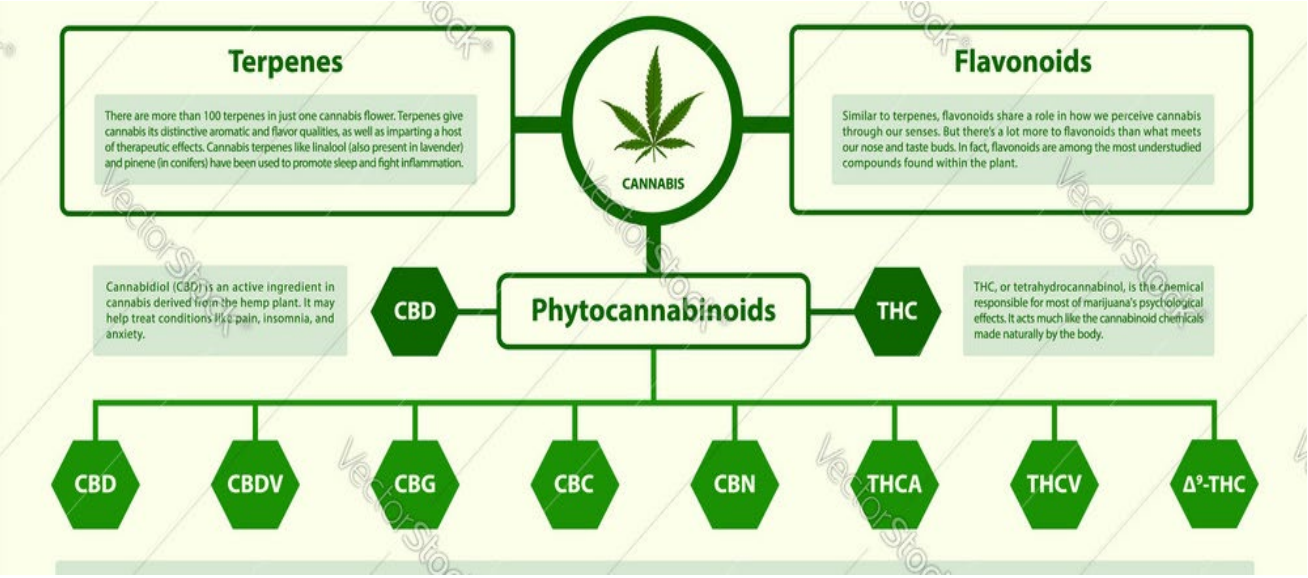


Whole Blood 11-OH-THC



THC + CBD Interactions in Edibles

- Two most common cannabinoids in edibles are THC and CBD
- Entourage Effect Theory (Russo, 2011)
- Often alleged that CBD can mitigate THC's negative effects. Evidence is mixed
- Implications for medical use of cannabinoids
  - Narrow therapeutic window of dronabinol



THC/CBD Drug-Drug Interactions

- Medical cannabis/CBD users often use other prescription medications
- THC and CBD are metabolized by cytochrome P450 enzymes, which are also the primary metabolic pathway of many medications. Potential for drug-drug interactions
- Few controlled clinical studies have characterized drug-drug interactions between THC/CBD and other medications

Study Design Overview

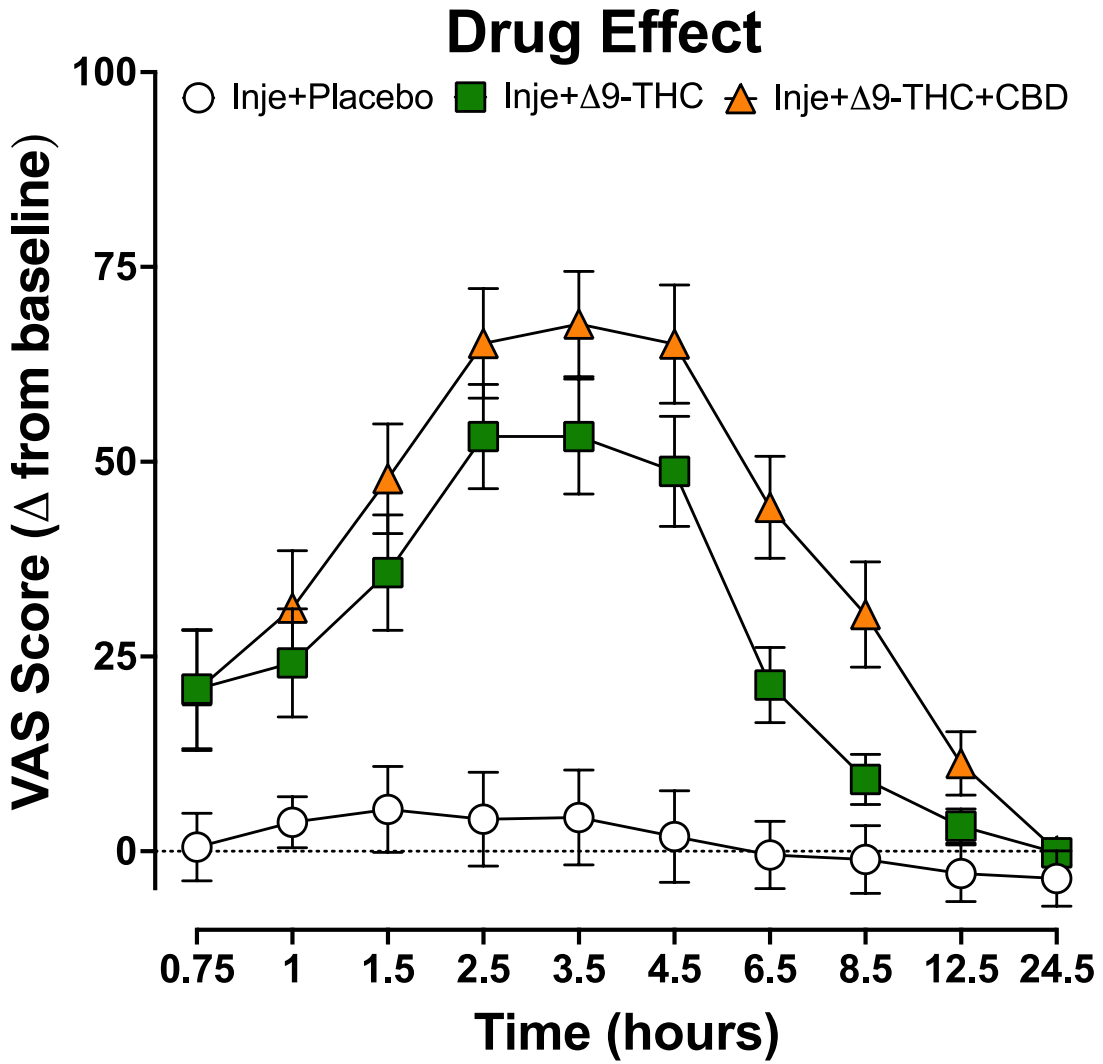
- Double blind, placebo controlled, randomized, crossover study
- Healthy adults completed 3 outpatient drug administration sessions:
  - Placebo Brownie
  - 20mg THC Brownie – high THC extract
  - 20mg THC + 640mg CBD Brownie – high CBD extract
- 30-min after consumption of the cannabis brownie, participants consumed a drug cocktail (the Inje cocktail) to probe 5 different CYP enzymes

Study Design Overview (cont.)

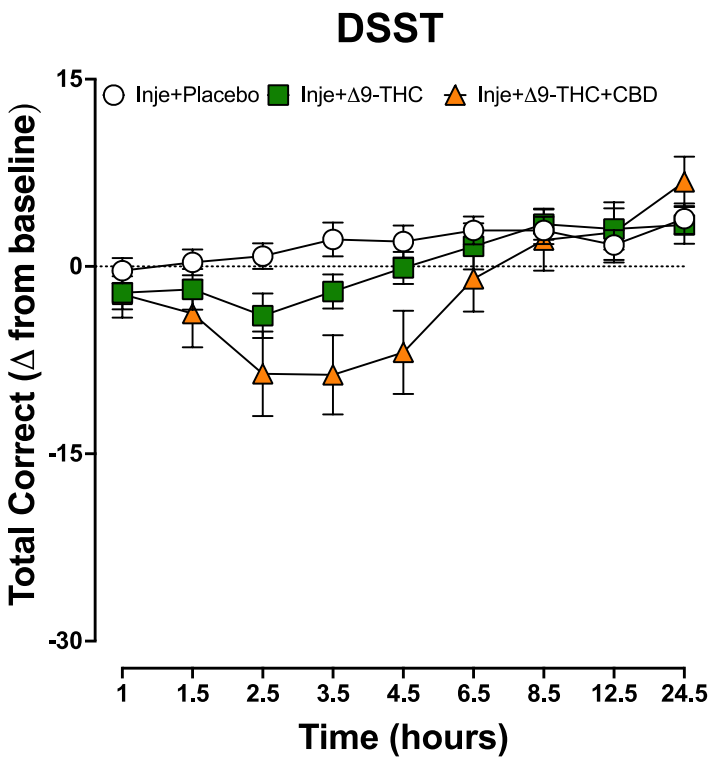
*all therapeutic or sub- therapeutic doses

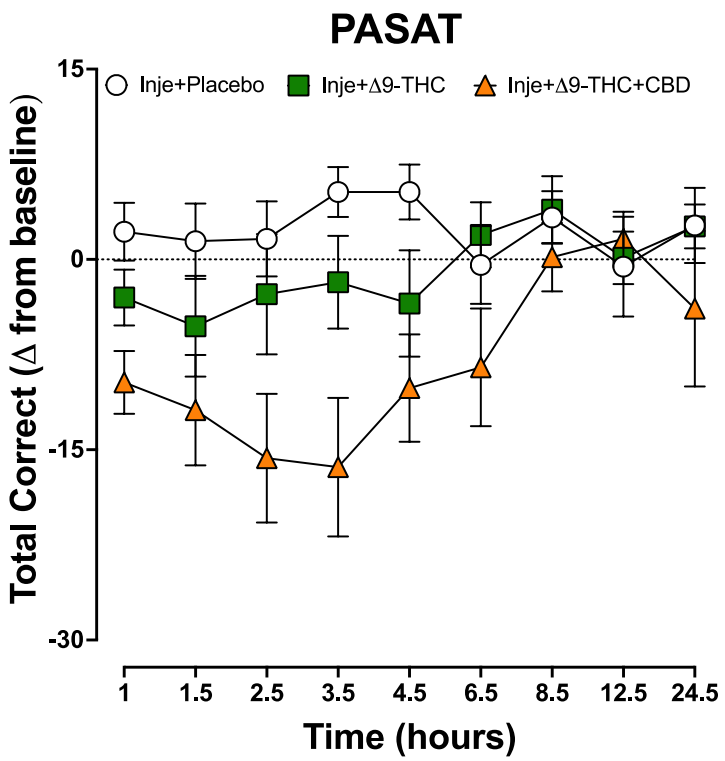
Caffeine	Stimulant present in coffee	100mg	CYP1A2
Losartan	Brand name: Cozaar; for hypertension	25mg	CYP2C9
Omeprazole	Brand name: Prilosec OTC; For heartburn and indigestion	20mg	CYP2C19
Dextromethorphan	Cough suppressant; in numerous cough medications	30mg	CYP2D6
Midazolam	Benzodiazepine; used most often for anesthesia	2mg	CYP3A

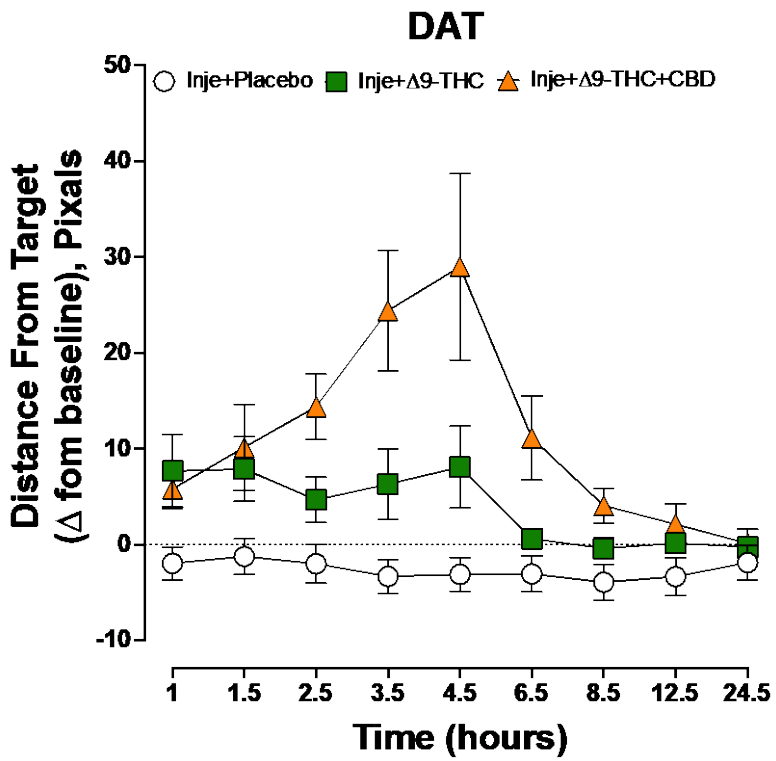
Subjective Ratings for “Drug Effect”



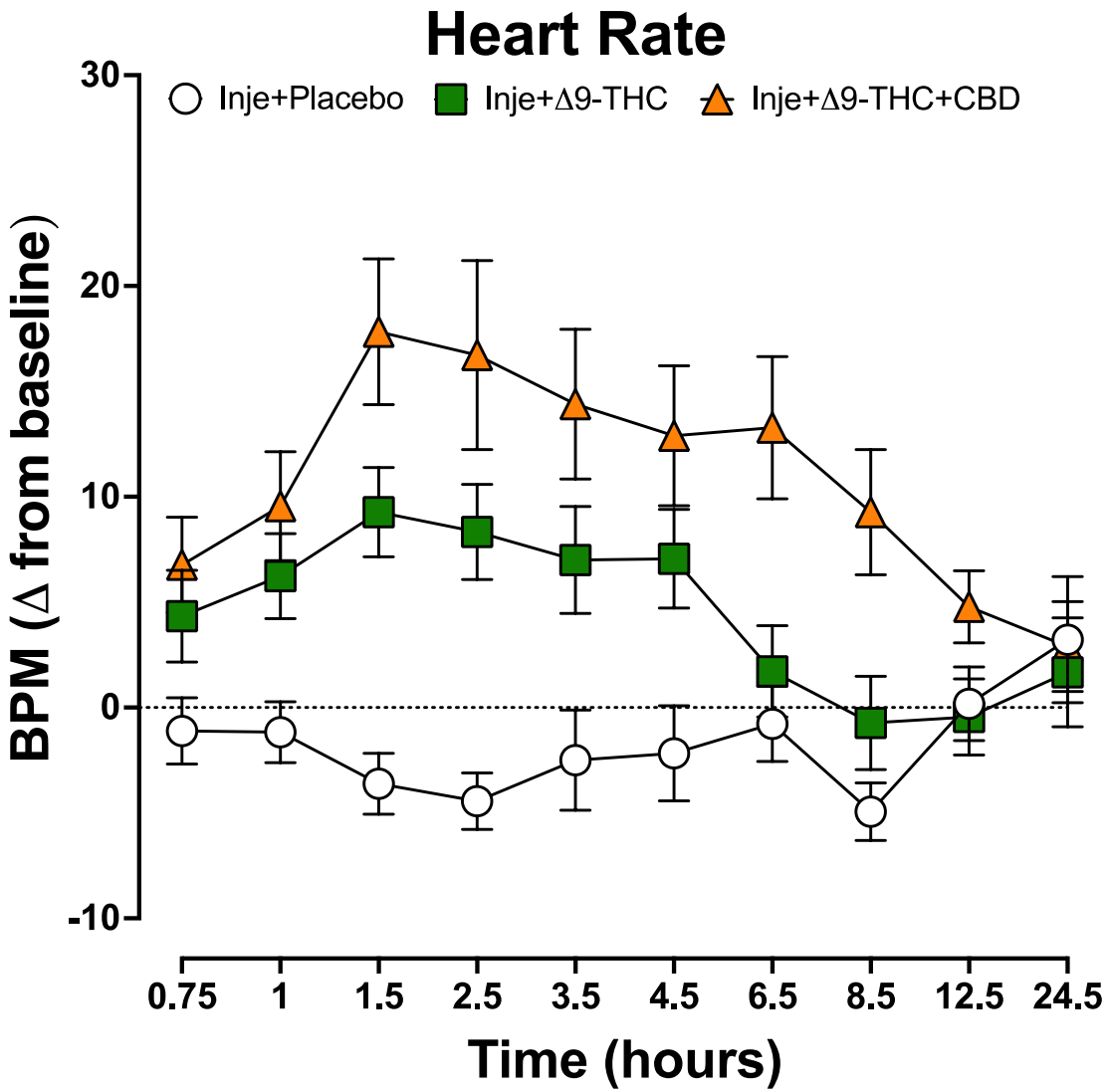
Cognitive Performance



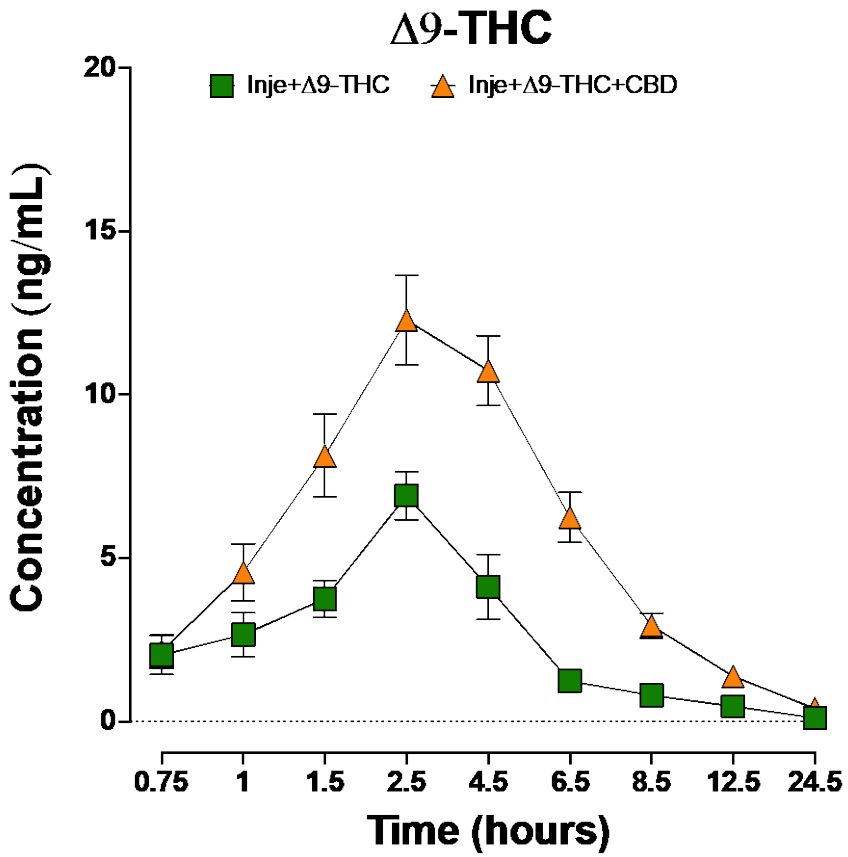


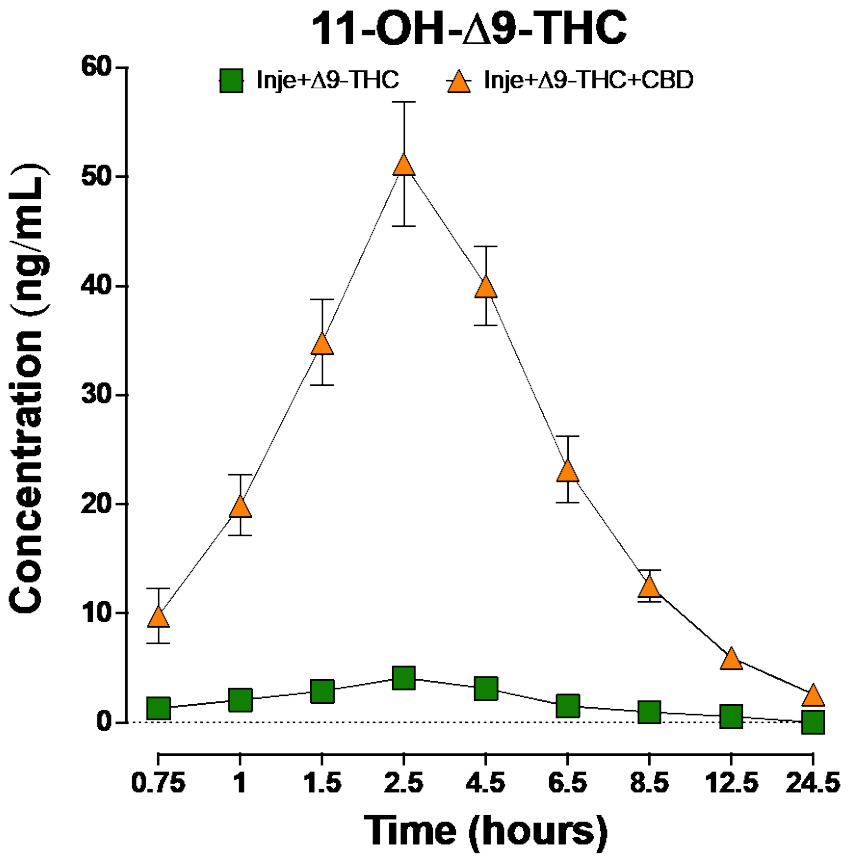


Heart Rate


Heart Rate
Inje+Placebo
Inje+Δ9-THC
Inje+Δ9-THC+CBD
BPM (Δ from baseline)
30
20
10
0
-10
0.75
1
1.5
2.5
3.5
4.5
6.5
8.5
12.5
24.5
Time (hours)

THC + Metabolites in Blood

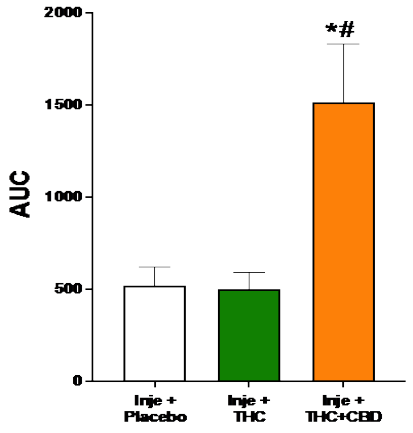




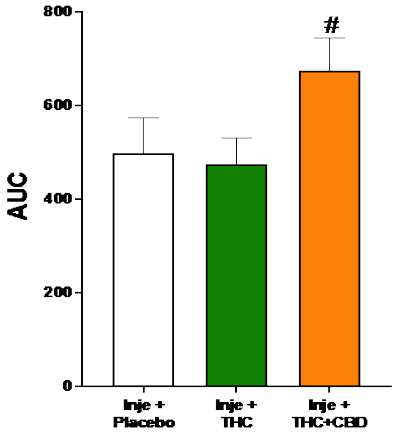
Inje cocktail & placebo
Inje cocktail & THC
Inje cocktail & THC + CBD

CYP2C19

Omeprazole

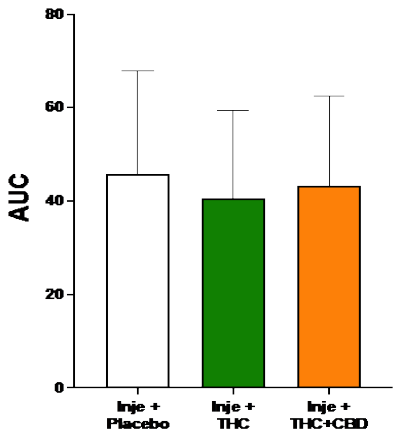


5-OH Omeprazole

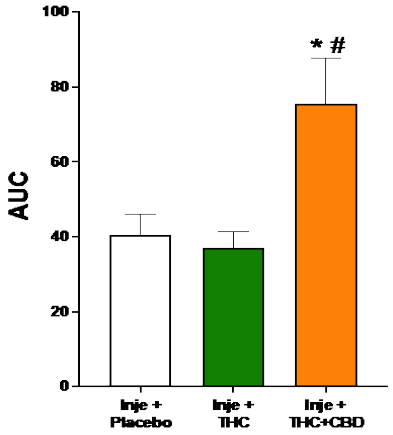


CYP2D6

Dextromethorphan

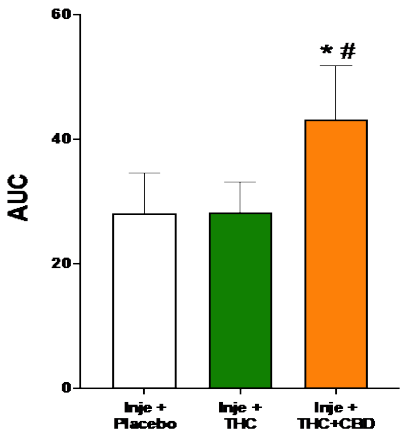


Dextrorphan

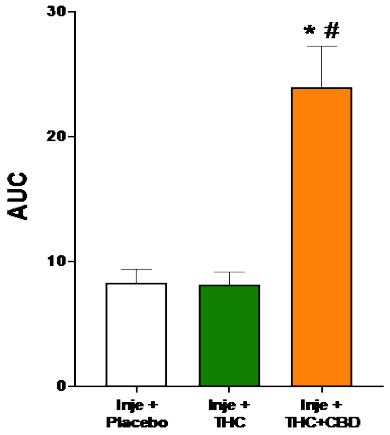


CYP3A

Midazolam

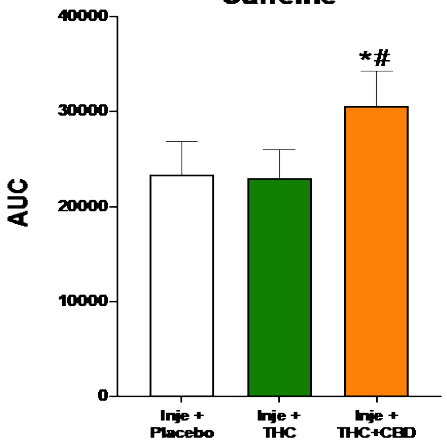


1-OH Midazolam

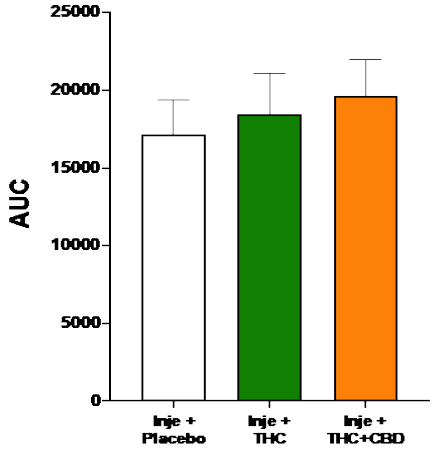


CYP1A2

Caffeine

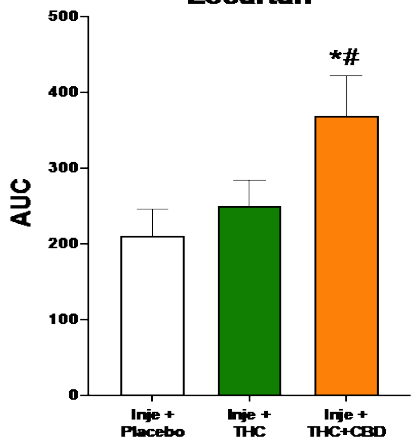


Paraxanthine

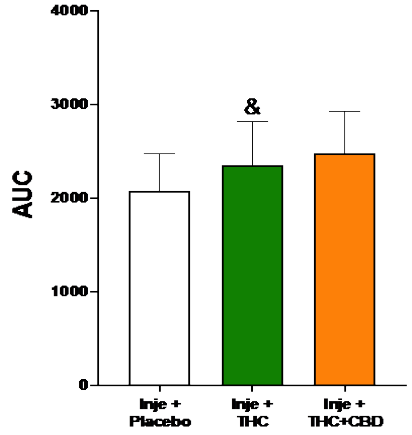


CPY2C9

Losartan

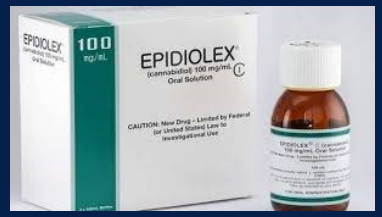


Losartan Carboxylic Acid

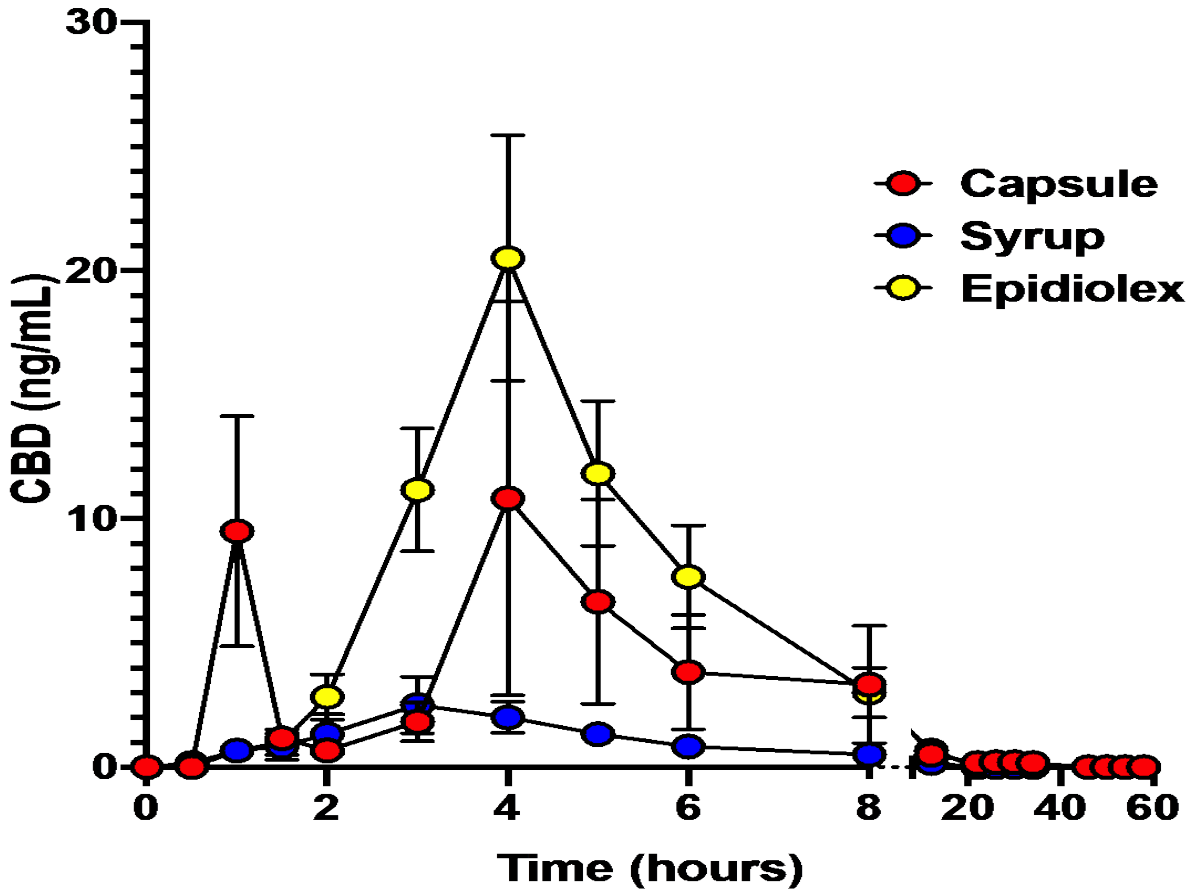


Many Different Oral Formulations

- The liquid vehicle or food matrix of oral products could impact bioavailability
- Three different oral solutions were administered in recent study – all contained 100mg CBD
- Capsule (N=6)
- Epidiolex (N=6)
- Syrup (used for commercial cough medications) (N=6)



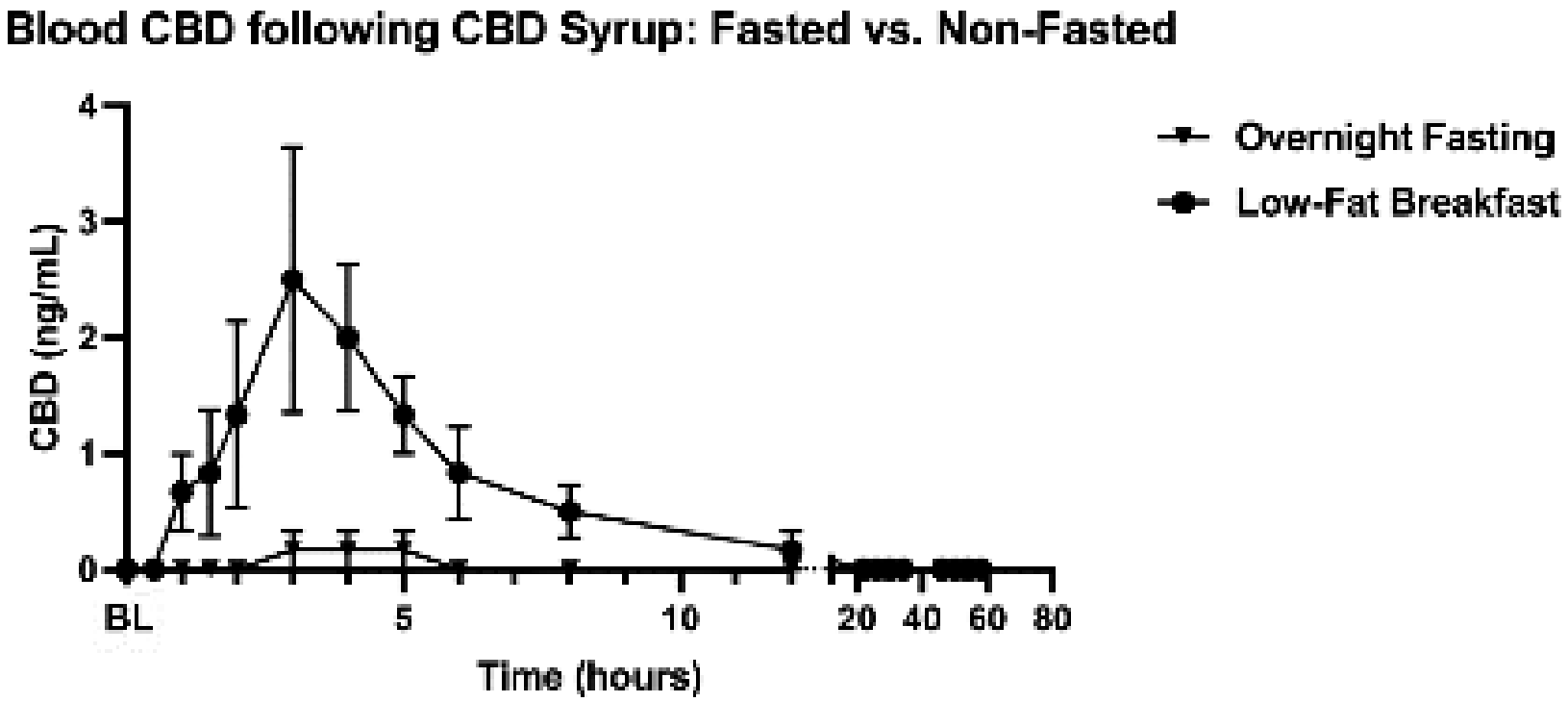
Blood CBD Concentrations by Oral Formulation



Data from: Bergeria et al., 2022, *Journal of Analytical Toxicology*

Dietary Factors

Ingesting CBD after fasting vs. with a low-fat meal.



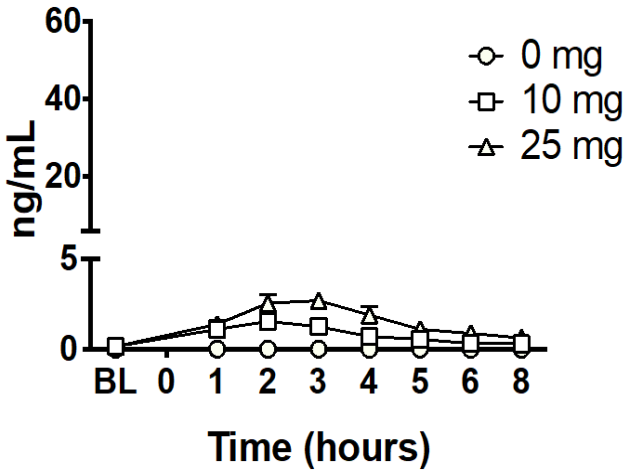
Data from: Bergeria et al., 2022, *Journal of Analytical Toxicology*

Measuring Cannabis Impairment

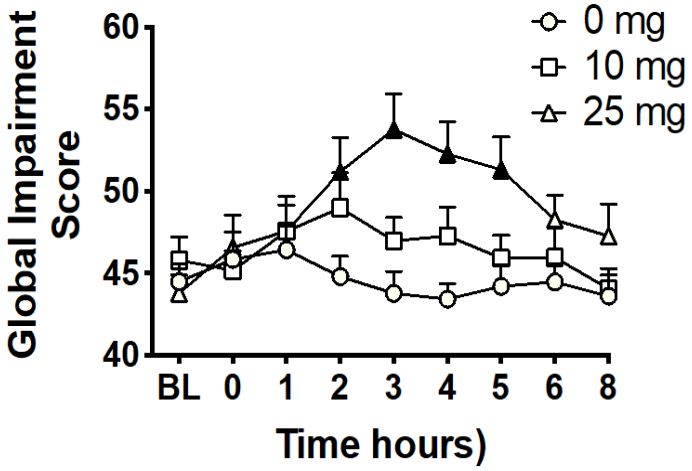
- With expanding legalization, the incidence of driving under the influence of cannabis (DUIC) is increasing
- Increasing need to be able to objectively detect cannabis impairment at the roadside and elsewhere
- Currently, the primary methods used to detect cannabis impairment at the roadside are:
  - Blood THC levels (i.e., per se limits or zero-tolerance thresholds)
  - Effects-based laws (i.e., field sobriety tests)
    - Are these effective for edibles?

Is Blood THC Related to Impairment?: Oral Cannabis

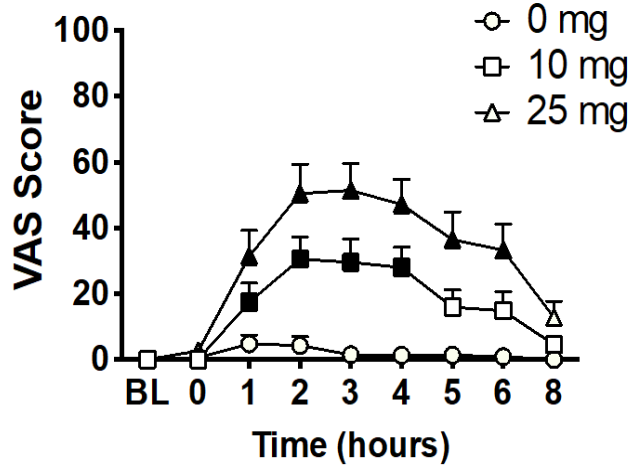
Whole Blood THC



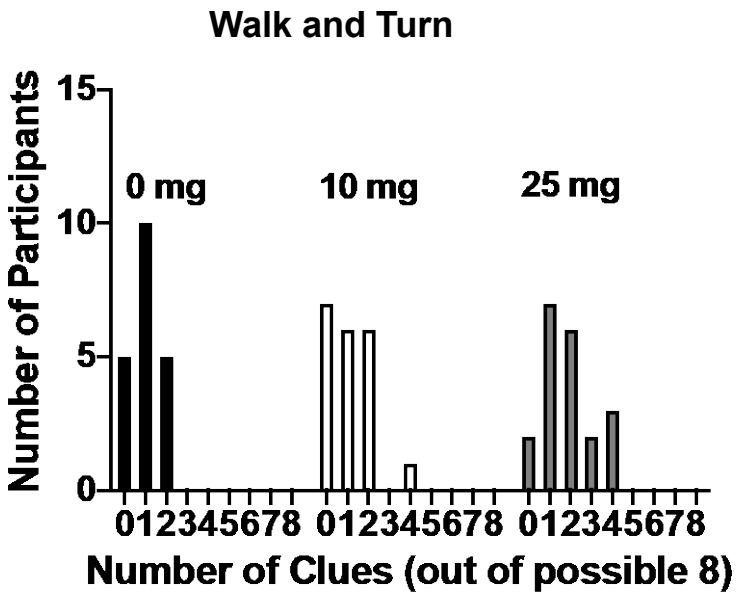
DRUID Impairment Score

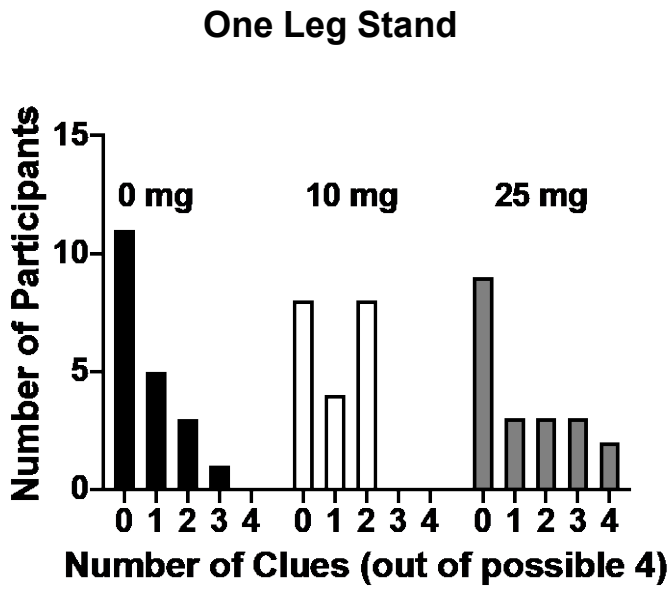


Subjective Ratings
"Feel Drug Effect "



Field Sobriety Tests





Next Steps: Simulated Driving Impairment Research

- Next Steps – new project that is examining interactive effects between cannabis edibles and alcohol on simulated driving performance
- Study 1: Oral cannabis + alcohol; Study 2: Vaporized cannabis + alcohol:
  - Placebo cannabis + Placebo alcohol
  - Low dose cannabis (10mg THC) + Placebo alcohol
  - High dose cannabis (25mg THC) + Placebo alcohol
  - Placebo cannabis + Alcohol (0.05% BAC)
  - Low dose cannabis (10mg THC) + Alcohol (0.05% BAC)
  - High dose cannabis (25mg THC) + Alcohol (0.05% BAC)
  - Placebo cannabis + Alcohol (0.08% BAC)

Overall Summary

- Cannabis edible effects are delayed, but of a similar magnitude to other routes of administration (e.g., smoked) at a given THC dose (important implications for dose titration and adverse events)
- CBD appears to exacerbate effects of THC, likely due to PK interactions when both are administered orally
- Oral THC/CBD have profound drug-drug interactions with other medications
- Product formulation and user diet greatly impacts cannabinoid absorption
- Novel approaches to measuring cannabis impairment are needed to detect cannabis-impaired drivers

Thank You!

- Collaborators: Ryan Vandrey, Ed Cone, Austin Zamarripa, Dennis Sholler, Elise Weerts, Ron Flegel, Eugene Hayes, Ruth Winecker
- Johns Hopkins BPRU and CRU nursing and research staff
- NIDA Drug Supply Program
- Study participants
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Cannabis Science Laboratory

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