Cannabinoids and Health

Module 16

Lecture 1: What have we learned?

What Have We Learned - THC - High Dose

- Not a single study suggests that high doses of THC are good for something
  - “High dose” depends on individual but generally > 1-2 grams per day of flower or > 35 mg/day in oral form

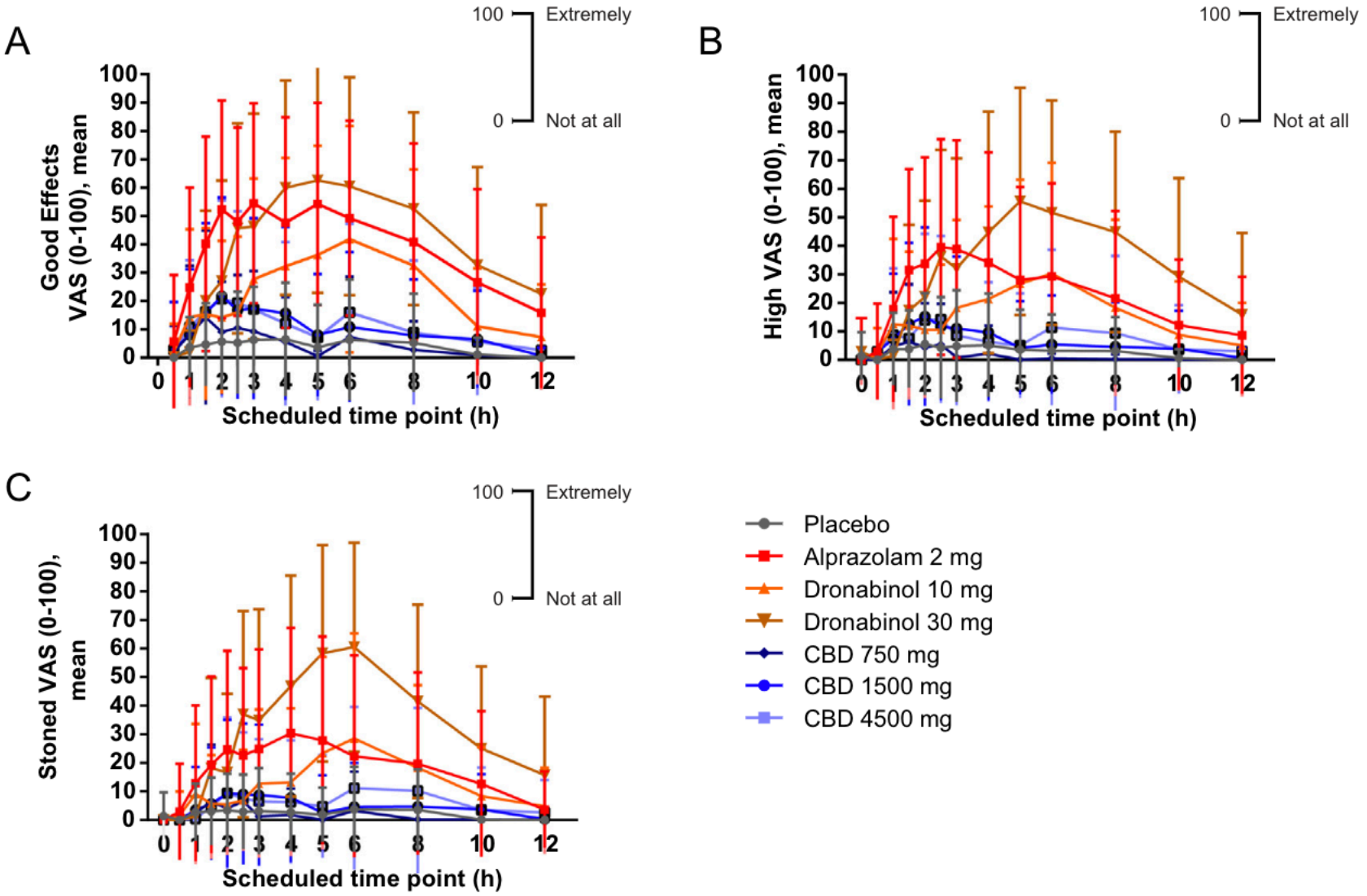
- High doses may be problematic in terms of altering the endocannabinoid system, downregulating CB1 receptors, impairing cognition, increasing risk of psychosis in young people, producing tolerance to beneficial effects (not much research on this yet)

THC - Low to Moderate Dose

- Not a single study suggesting that low doses of THC are bad
  - “low dose” depends on individual but generally < .25 gram of flower or < 2.5 mg in oral form
- Some studies (in animals) suggest that low doses, and very low doses (< 1 mg) may have positive effects (anti-aging)
- Also, studies suggest that moderate doses (5 – 10 mg) can have positive effects when combined with CBD (e.g., sativex)
- Low to moderate doses of THC are probably a critical component – especially in terms of pain and opioid sparing effect and early research suggests it may be important for anxiety

CBD – Very High Dose

- High doses (e.g., 20 mg/kg or about 1500 mg per day) associated with elevated liver enzymes
- High doses also impact drug metabolism thereby interacting with other medications (more research needed)
- These two findings come mainly from Epidiolex data in children
- Otherwise acute effects of high doses (one study tested up to 4500 mg) seem to be fairly benign
  - Interesting that none of the GW pharma studies report THC blood levels


A
Good Effects VAS (0-100), mean
100 Extremely
0 Not at all
Scheduled time point (h)
B
High VAS (0-100), mean
100 Extremely
0 Not at all
Scheduled time point (h)
C
Stoned VAS (0-100), mean
100 Extremely
0 Not at all
Scheduled time point (h)
Placebo
Alprazolam 2 mg
Dronabinol 10 mg
Dronabinol 30 mg
CBD 750 mg
CBD 1500 mg
CBD 4500 mg

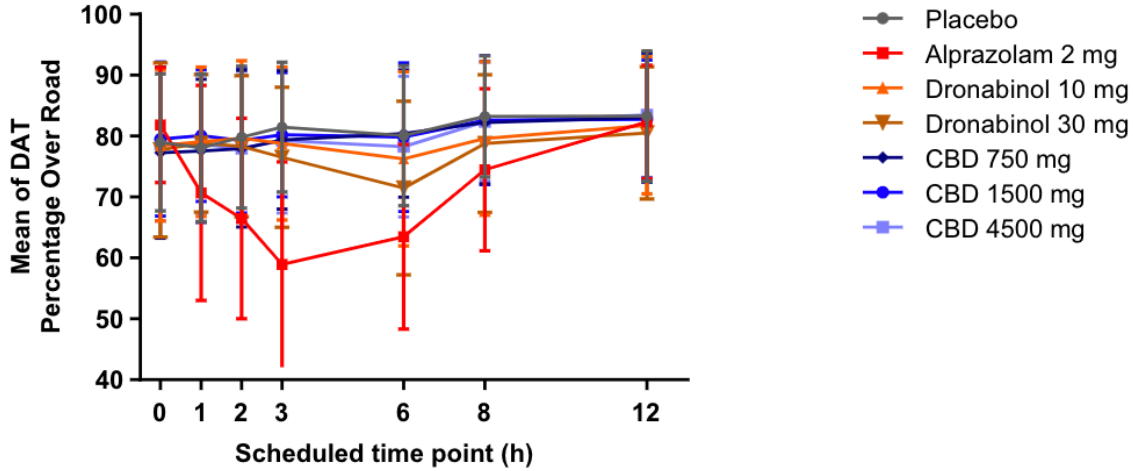


Fig. 5. Time-response profile for cognitive and psychomotor effects of CBD, alprazolam, dronabinol, and placebo. Divided Attention Test — Percentage Over Road values (mean ± standard deviation). CBD, cannabidiol; DAT, Divided Attention Test.

Table 2
Pharmacokinetic parameters of CBD.

PK parameter	CBD 750 mg (N = 38)	CBD 1500 mg (N = 39)	CBD 4500 mg (N = 40)
C_{max}, ng/mL Mean (% CV)	336.2 (46.7)	524.5 (64.9)	426.9 (112.8)
T_{max}, h Median (range)	5.11 (2.18–8.23)	6.13 (3.13–8.17)	4.07 (2.15–12.20)
$AUC_{(0\text{-last})}$, h·ng/mL Mean (% CV)	1586.7 (52.0)	2649.6 (70.1)	2338.6 (109.6)
$AUC_{(0\text{-}\infty)}$, h·ng/mL Mean (% CV)	1683.3 (46.7) (n = 34)	2713 (64.0) (n = 27)	2290.3 (104.1) (n = 31)

$AUC_{(0\text{-last})}$, area under the plasma concentration-time curve from time zero to the last measurable concentration; $AUC_{(0\text{-}\infty)}$, area under the plasma concentration-time curve from time zero to infinity; CBD, cannabidiol; C_{max}, maximum plasma concentration; % CV, percentage coefficient of variation; N, number of subjects in the PK population for a given treatment; n, number of values included in the calculation of summary statistics; T_{max}, time to maximum observed plasma concentration.

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Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans

Alex F. Manini, MD, MS[1], **Georgia Yiannoulos, MS**[2], **Mateus M. Bergamaschi, PhD**[3], **Stephanie Hernandez, MD, MS**[1], **Ruben Olmedo, MD**[1], **Allan J. Barnes, BSc**[4], **Gary Winkel, PhD**[5], **Rajita Sinha, PhD**[6], **Didier Jutras-Aswad, MD, MS**[7,8], **Marilyn A. Huestis, PhD**[4], and **Yasmin L. Hurd, PhD**[2]

[1]Division of Medical Toxicology, Department of Emergency Medicine, The Icahn School of Medicine at Mount Sinai, New York, NY, USA

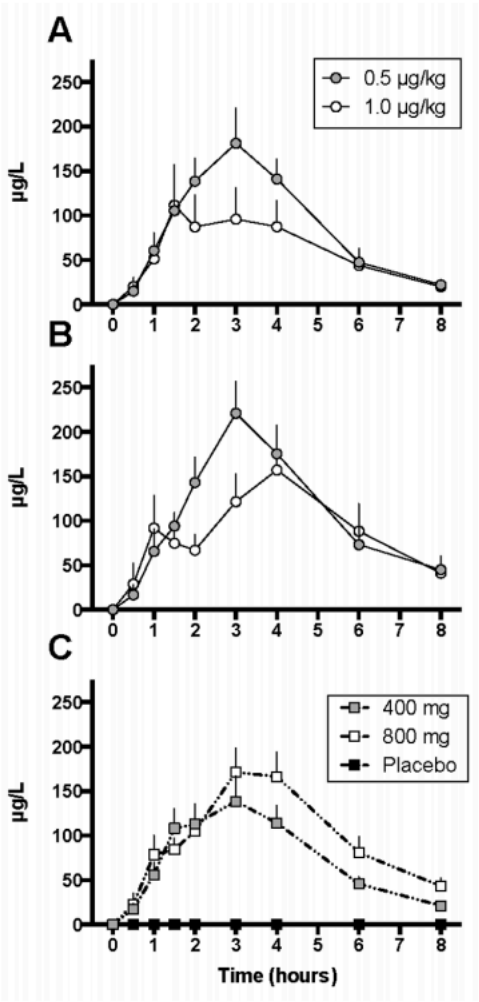

Figure 2. Plasma CBD Concentrations

Mean (± SEM) plasma CBD concentrations across time (in hrs) were not significantly affected by Fentanyl dose (AUC Wilcoxon p=NS). Mean (± SEM) plasma CBD concentrations for Low-Dose (400 mg) CBD are in **Panel A** and High-Dose (800 mg) CBD is in **Panel B. Panel C** represents the combined curves for all Groups (0, 400mg and 800 mg

Table 3

Subjective Measures Analysis by Treatment Group

Treatment Group	PANAS		OVAS
	Positive*	Negative	
CBD 0mg- 0.5 Fentanyl	33.56	10.04	19.17
CBD 0mg- 1.0 Fentanyl	31.50	10.04	19.61
CBD 400mg-0.5 Fentanyl	23.81	10.08	18.44
CBD 400mg-1.0 Fentanyl	23.10	10.25	17.52
CBD 800mg-0.5 Fentanyl	33.85	10.81	24.56
CBD 800mg-1.0 Fentanyl	33.06	10.40	23.92

400 mg of CBD decreases positive affect but 800 does not?

Mean scores for the subjective measures (PANAS, OVAS) and the results of the repeated measures statistical analysis.

* Mixed linear model with repeated measures.

Abbreviations: OVAS=Opiate Visual Analog Scales; PANAS=Positive and Negative Affect Scales; S=session number.

CBD – Importance of Dose

- For sleep, dose of 160 mg seemed to produce an effect
- A couple of small studies on anxiety suggested that 300 mg showed an effect
- Yasmin Hurd's work on opioid use was done with 400 – 800 mg
- Two studies on psychosis used 600-1000 mg
- Epilepsy literature suggests that it takes about 20 mg/kg (or 1500 mg for average person)
- CBD craze across the nation
  - Mostly sold in doses of 5-20 mg
  - No evidence (yet) that 5-20 mg does anything

CBD – Importance of Dose

- Caveat is that nobody is studying lower doses
- New studies need to include a low dose – would be good as a control if nothing else
- Also important to note
  - Not a single study (that I know of) suggesting that CBD is bad for you

The Job of a Scientist

- Is more than just understanding the research that has been done
- Job is to synthesize research in ways that leads to new theories, new hypotheses, and new knowledge
- Low doses of THC seem to be important and not harmful
- Higher doses of CBD (>100 mg) seem to be important and not harmful
- There are no studies suggesting that combining CBD with THC is a bad idea (i.e., CBD does not take away something useful from THC)
- If you want to avoid intoxication and you want a combination of THC and CBD, the dose of THC is the limiting factor
- 1 – 10 mg of THC, combined with 100-1000 mg of CBD are probably the doses that should be studied

20:1 Ratio of CBD to THC*

THC Dose (mg)	CBD Dose (mg)
1	20
2.5	50
5	100
10	200

*Hemp derived products are generally in the range of 20:1 to 30:1. If you take a Hemp derived product with 100 mg of CBD, you will likely get around 5 mg of THC.

50:1 Ratio of CBD to THC

THC Dose (mg)	CBD Dose (mg)
1	50
2.5	100
5	250
10	500

100:1 Ratio of CBD to THC

THC Dose (mg)	CBD Dose (mg)
1	100
2.5	250
5	500
10	1000

Summary

- We understand the risks and benefits by THC dose pretty well
- We really do not understand CBD dosing yet
  - OTC doses are probably so low that they are close to a placebo
  - Dose effects likely varies by condition but be in the range of 100-1000+ (total speculation)
- THC may be important and low dose seems pretty safe
  - 1 to 5 mg combined with 100+ mg of CBD?