Medicinal Cannabis

Penn State College of Medicine Grand Rounds
January 28, 2021

Igor Grant, MD, Director

Co-Directors
J. Hampton Atkinson, MD & Thomas D. Marcotte, PhD

www.cmcr.ucsd.edu
Cannabis sativa (C. sativa)

Cannabis sativa L. A) Flowering male staminate. B) Fruiting female pistillate plant:

1 male staminate flower;
2 stamen (anther and short filament);
3 stamen; 4 pollen grains;
5 female pistillate flower with bract;
6 female flower without bract;
7 female flower showing ovary, longitudinal section;
8 fruit (the fruit is the seed, technically achene) with bract;
9 fruit without bract;
10 fruit (side view);
11 fruit (cross-section);
12 fruit (longitudinal section);
13 fruit without pericarp (hulled).
Marijuana Compounds

Isolation, structure and partial synthesis of an active constituent of hashish.

Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil
Cannabis: not a new medicine
Cannabis Legalization by State, Jan 2021

https://commons.wikimedia.org/wiki/User:Lokal_Profil
Cannabis Comes in from the Cold: A Tale of Science and Politics

- Persistent anecdotal reports of benefits
- Political shifts favoring medicinal access (in the United States, most states now provide for some measure of access)
- Discovery of the endocannabinoid system
  - CB1 and CB2 receptors
  - Anandamide\(^1\)
  - \(2\text{-arachidonoylglycerol}\)\(^{2,3}\) and other signaling molecules
  - Development of synthetic molecules: agonists, partial agonists, antagonists, and other modifiers (e.g., inhibitors of fatty acid amide hydrolase [FAAH]. FAAH breaks down anandamide)

“Circuit Breaker” Function of CB Receptors

Neurotransmitter (e.g., glutamate) action on post synaptic cells triggers them to release endocannabinoids (EC) that act on presynaptic CB receptors to regulate neurotransmission. The EC are then inactivated by FAAH or MGL.*

* FAAH = fatty acid amide hydrolase     MGL = monoglyceride lipase  (Courtesy D. Piomelli, UCI)
University of California
Center for Medicinal Cannabis Research (CMCR)

Igor Grant, MD, Director

Co-Directors
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Investigators
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Senior Staff
Jennifer Marquie-Beck, MPH, Felicia Roston, Carla Ingle, Clint Cushman, Debra Cookson, MPH

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<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>November 1996</td>
<td>California Prop 215 passes: Compassionate Use Act</td>
</tr>
<tr>
<td>August 2000</td>
<td>Center for Medicinal Cannabis Research established at the University of California, San Diego</td>
</tr>
<tr>
<td>September 2003</td>
<td>Amendment to Medical Marijuana Research Act of 1999, sunset restrictions removed. (SB 295)</td>
</tr>
<tr>
<td>November 2016</td>
<td>Proposition 64 allocates $2M/yr to CMCR to continue its mission</td>
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</tbody>
</table>
Because Cannabis Is a Schedule 1 Drug, and the Only Legal Source Is the Federal Government, Medical Studies Are Challenging

**DEVELOP DETAILED PROTOCOL**

*(identify drug source)*

**Scientific/Funding Approval**

**LOCAL:**

IRB

**FEDERAL:**

IND *(FDA)*

**IRB Approval Pending**

**CALIFORNIA:**

RAPC

**REVISED APPROVED PROTOCOL**

**30 Day Review**

**FEDERAL:**

Schedule 1 License *(DEA)*

**LOCAL:**

Site Inspection *(DEA)*

**ORDER PRODUCT**

*NIDA or other supplier*

**BEGIN STUDY**

Time from submission of CMCR-approved study to state and federal regulators to study initiation was ~1 year (range, 6-18 months).

CMCR = UCSD Center for Medicinal Cannabis Research; DEA = Drug Enforcement Administration; DHHS = Department of Health & Human Services; FDA = Food and Drug Administration; HQ = headquarters; IND = investigational new drug; NIDA = National Institute on Drug Abuse; RAPC = Research Advisory Panel of California; SRB = scientific review board.
# DEA Scheduling

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>No currently accepted medical use and high potential for abuse</td>
</tr>
<tr>
<td>II</td>
<td>High potential for abuse, potentially leading to dependence</td>
</tr>
<tr>
<td>III</td>
<td>Moderate to low potential for physical and psychological dependence</td>
</tr>
<tr>
<td>IV</td>
<td>Low potential for abuse or dependence</td>
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<tr>
<td>V</td>
<td>Lower abuse risk than IV, limited quantities of narcotics; (antidiarrheal, analgesic)</td>
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</table>

## THC

<table>
<thead>
<tr>
<th>Plant/ Synthetic</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<tr>
<td>Plant</td>
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<tr>
<td>Synthetic</td>
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<tr>
<td>Nabilone (Cesamet)</td>
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<tr>
<td>Dronabinol (Syndros)</td>
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<tr>
<td>Dronabinol (Marinol)</td>
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## CBD

<table>
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<th>Plant/ Synthetic</th>
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<td>Plant*</td>
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<tr>
<td>Synthetic*</td>
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<tr>
<td>Epidiolex</td>
<td></td>
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<tr>
<td>Hemp^</td>
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</tbody>
</table>

* > 0.3% THC content  
^ No detectable THC  
^ THC content 0.3% or less  

CMCR  
UC San Diego  
CENTER FOR MEDICINAL CANNABIS RESEARCH
Study Locations

UCSD
UC-Davis
UC-Merced
UCSF
San Mateo

UCLA
UC-Irvine
UCSD
CMCR Abrams et al study: Cannabis reduces HIV Neuropathic Pain

Placebo controlled double blind randomized trial of 4% THC containing vs 0% THC MJ cigarettes administered 3x/day for 5 days.

# CMCR Clinical Studies completed

<table>
<thead>
<tr>
<th>SITE</th>
<th>DISORDER</th>
<th>DESIGN</th>
<th>N</th>
<th>DOSE (% THC)</th>
<th>Result</th>
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<tbody>
<tr>
<td>Mark Wallace</td>
<td>Healthy Volunteers (Experimentally-Induced Pain)</td>
<td>Crossover RCT</td>
<td>15</td>
<td>0%, 2%, 4%, 8%</td>
<td>+</td>
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<td>UCSD</td>
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<tr>
<td>Donald Abrams</td>
<td>HIV Neuropathy, Experimental Pain</td>
<td>Parallel Groups RCT</td>
<td>50</td>
<td>0%, 3.5%</td>
<td>+</td>
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<tr>
<td>UCSF</td>
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<tr>
<td>Ronald Ellis</td>
<td>HIV Neuropathy</td>
<td>Crossover RCT</td>
<td>28</td>
<td>0%, 1-8%</td>
<td>+</td>
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<tr>
<td>Barth Wilsey</td>
<td>Neuropathic Pain, Experimental Pain</td>
<td>Crossover RCT</td>
<td>33</td>
<td>0%, 3.5%, 7%</td>
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<td>UC Davis</td>
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<tr>
<td>Barth Wilsey</td>
<td>Neuropathic Pain</td>
<td>Crossover RCT</td>
<td>39</td>
<td>0%, 1.29%, 3.53% (Vaporized)</td>
<td>+</td>
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<tr>
<td>UC Davis</td>
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<tr>
<td>Jody Corey-Bloom</td>
<td>MS Spasticity</td>
<td>Crossover RCT</td>
<td>30</td>
<td>0%, 4%</td>
<td>+</td>
</tr>
<tr>
<td>UCSD</td>
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<tr>
<td>Mark Wallace</td>
<td>Diabetic Neuropathy</td>
<td>Crossover RCT</td>
<td>16</td>
<td>0%, 2%, 4%, 7%</td>
<td>+</td>
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<tr>
<td>UCSD</td>
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</tbody>
</table>
Current and Pending CMCR Studies

1. Vaporized cannabis and dronabinol in low back pain
2. Oral THC/CBD in essential tremor
3. CBD in severe autism
4. CBD in schizophrenia
5. Vaporized cannabis in neuropathic pain
6. Effects of THC and CBD on endocannabinoids in bipolar
7. CBD in rheumatoid arthritis
8. CBD for sleep disorders
9. CBD for anorexia nervosa
10. Cannabigerol, THC, CBD in pain
11. Cannabis effects on driving
12. CBD to reduce alcohol craving (rodent)
13. CBD effects on blood pressure and metabolic syndrome (rodent)
How effective is cannabis relative to other pain medications? Number-Needed-to-Treat

- Number-Needed-to-Treat (NNT) = 1/Proportion improved in experimental condition – Proportion improved on placebo

- Ex: If 30% reduction in pain intensity = “Improved” and 60% “improve” in the experimental condition, while 30% “improve” in the placebo condition, then 0.60 – 0.30 = 0.30 and

NNT = 1/.30 = 3.3
**Common Analgesics for Neuropathic Pain**

- **Tricyclics**: 2.2
- **Cannabis**: 3.6
- **Gabapentin**: 3.7
- **Lamotrigine**: 5.4
- **SSRIs**: 6.7

*Number Needed to Treat to achieve a 30% reduction in pain.*
Optimal dosage?: Therapeutic window?

Low-dose inhaled THC (~1.5%) resulted in equivalent analgesia to ~4% with minimal psychotropic effects in patients with neuropathic pain

Greatest analgesia at mid-range dose (ng/ml) in participants with painful diabetic peripheral neuropathy suggests a therapeutic window


Wallace, M. et al. (In submission)
Evidence for Therapeutic Benefits of Cannabis

- **Substantial/conclusive evidence of cannabinoid efficacy in:**
  - chronic pain
  - Spasticity of multiple sclerosis
  - Control of nausea

- **Moderate evidence of cannabinoid efficacy in:**
  - Improving sleep in those with chronic medical conditions, eg., chronic pain, fibromyalgia etc.

- **Limited evidence of cannabinoid efficacy in**
  - Treatment of certain anxiety disorders and PTSD
  - Promoting appetite and weight gain

- **No or insufficient evidence of cannabinoid efficacy in**
  - Treatment of cancers, irritable bowel syndrome, epilepsy, movement disorders due to Huntington Disease or Parkinson Disease, Schizophrenia

Cannabis May Reduce Opioid Use States With and Without Medicinal Cannabis

Reduced Daily Doses Annually per Physician

Lower Opioid Overdose Mortality Rates

Bachhuber et al., 2014; JAMA Internal Med

Reduced Annual Medicare Spending

Bradford & Bradford, 2016
Decrease in other prescription drug use over the course of 6 months when cannabis integrated into treatment

Lucas et al., 2020 Pain Medicine
Although it may be effective, smoked marijuana as medicine presents challenges

- Safety of combustible material in clinical setting
- Second hand smoke as an irritant, possibly health hazard
- Efficiency and tolerability in smoking naïve
- Availability of cigarettes with standardized dose
- Conflict with anti drug laws
- Possibility of misuse and diversion
- Difficulty in conducting clinical trials on Schedule I substance whose legal availability is limited
Mode of Administration Matters: Need to compare efficacy, duration of beneficial and untoward effects

**Inhaled vs. Edible**


**Smoked vs. Vaporized**

Devices for Marijuana Vaporization

E-cigarettes

Volcano®

Courtesy David Gorelick, MD
Alternative Delivery Systems: “Volcano”

- Cannabis heated to 180°C
- Below the point of combustion (230°C)
- Releases cannabinoids as vapor into balloon
- Inhaled via mouthpiece attached to balloon

STORZ & BICKEL GMBH & CO. KG
CMCR Wilsey vaporizer study: Low dose THC containing cannabis reduces neuropathic pain

Placebo controlled randomized crossover study of 39 patients with neuropathic pain of mixed etiology treated 2x/d. THC conc. = 0%; 1.3%; 3.5%

Nabiximols (Sativex®) oral mucosal spray

- Pump action oral mucosal spray
- Delivers 0.1 ml per spray of solution containing 25 mg/ml THC and 25 mg/ml CBD
- Derived from botanical sources, thus contains other cannabinoids and non-cannabinoids (e.g., flavonoids; terpenes)

Image courtesy G. Guy, GW Pharmaceuticals
Nabiximols (Sativex®) for Neuropathic Pain

Reduction of global neuropathic pain NRS scores in the two groups during the trial. Weekly mean pain scores were obtained from pain diaries.

Other Cannabinoids: Cannabidiol

Terpene phenolic heterocyclic structures of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

*Not active at CB1 or CB2

No psychoactive effect

Other Cannabinoids: Minor cannabinoids and suggested therapeutic potentials

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>Examples of potential medical application</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBG-A (Cannabigerolic acid)</td>
<td>Metabolic disorders, colon cancer</td>
</tr>
<tr>
<td>THC-A (Tetrahydrocannabinolic acid)</td>
<td>Arthritis, neurodegenerative diseases, nausea, appetite loss</td>
</tr>
<tr>
<td>CBD-A (Cannabidiolic acid)</td>
<td>Chemotherapy-induced nausea/vomiting (CINV), depression</td>
</tr>
<tr>
<td>CBC-A (Cannabichromene acid)</td>
<td>Fungal diseases</td>
</tr>
<tr>
<td>CBG (Cannabigerol)</td>
<td>Crohn’s disease, bowel disease, certain cancers</td>
</tr>
<tr>
<td>CBD-V (Cannabidivarin)</td>
<td>Seizure prevention, Rett syndrome, Duchenne muscular dystrophy (DMD)</td>
</tr>
<tr>
<td>CBC-V (Cannabichromevarin)</td>
<td>Osteoporosis, ALS, Muscular dystrophy</td>
</tr>
<tr>
<td>CBC (Cannabichromene)</td>
<td>Could inhibit growth of cancer cells, osteoarthritis, neurological diseases</td>
</tr>
<tr>
<td>THC-V (Tetrahydrocannabivarin) *</td>
<td>Diabetes, anxiety, PTSD, Alzheimer’s disease</td>
</tr>
<tr>
<td>CBN (Cannabinol) *</td>
<td>Bacterial infections, ALS, appetite stimulant</td>
</tr>
</tbody>
</table>

* These are psychoactive. The other minor cannabinoids are not psychoactive.
Cannabidiol - CBD

- Natural component of the Cannabis plant
- Constitutes up to 40% of marijuana extracts
- Devoid of typical psychological effects of THC
- Suggested applications as:
  - Anti-inflammatory
  - Analgesic
  - Anti-emetic
  - Hypnotic and sedative
  - Drug abuse treatment
  - Antipsychotic
  - Anticonvulsive
  - Neuro-protective
  - Anxiolytic
  - Others

- Antagonism of THC when both contents are administered concomitantly? FAAH inhibition?

Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil
Possible mechanisms of action of CBD

» Does not activate CB1 or CB2

» Desensitizes transient receptor potential channels, e.g., TRPV1: anti-nociceptive to inflammatory pain?

» Blocks GPR55, which may also play a role in neuropathic and inflammatory pain

» Enhances glycine receptor activity: anticonvulsant?

» Inhibits FAAH: increasing availability of anandamide?

» Enhances 5HT1A receptor: anxiolytic effect?

» Modulates cytochrome P4502C metabolism of THC to more psychoactive 11-OH THC?
Cannabidiol (CBD) Significantly Reduces Convulsive Seizure Frequency in Lennox-Gastaut Syndrome (LGS)

- 120 children/young adults
- 20 mg/kg CBD
- 14-week treatment period
- % with > 50% reduction in frequency (CBD – 43%; Placebo - 27%)
- AEs (diarrhea, vomiting, fatigue, etc.)

Devinsky et al., 2017 (NEJM)
Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients

Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil.
CBD Improves Positive and Negative Symptoms of Schizophrenia

42 cases randomized to receive 800 mg/d CBD or amisulpride

PANSS = Positive and Negative Syndrome Scale.

Data show predicted means and side effects. Statistical significance is calculated between groups and versus baseline, that is, 0 (*CBD, #AMI; #P \leq 0.001; ***/###P \leq 0.05).

Compared to Atypical Antipsychotic Amisulpride, CBD Does Not Worsen Extrapyramidal Symptoms, and Is Not Associated with Weight Gain or Elevated Prolactin

Data show predicted means and side effects. Statistical significance is calculated between groups (\(††P \leq 0.01, †††P \leq 0.001\) and versus baseline, that is, 0 (*CBD, #AMI; ‡‡P \leq 0.01; ‡‡‡P \leq 0.05; */#P \leq 0.001).)

CBD attenuates nicotine withdrawal

Nicotine = 3.14 mg/kg/day
Cannabidiol (Noramco) = 30 mg/kg, s.c.
180-300 ng/ml (blood)

Data courtesy of Giordano de Guglielmo, PharmD, PhD and Olivier George, PhD, UCSD
What are the downsides of medicinal cannabis?

» Acute effects: alertness; cognitive; mood; cardiovascular
  • Effects on driving, work, studying?
  • Some of these effects wear off (habituation) with regular use

» Longer term use: long term effects of cannabinoids as medicines unknown. Data from recreational use:
  • Moderate use in adults not associated with organ system injury* based on 2017 National Academies review. However:
    • Effects on youth, eg., developing brain, unclear. Many negative effects reported, eg., IQ loss, psychosis risk, but “chicken vs egg” conundrum
    • Effects in other groups? eg., elderly, underlying conditions

» Interactions with other medicines/drugs: clear amplification of neurocognitive effects; other pharmacologic interactions unclear.
Meta-analyses of cannabis intoxication and automobile crashes (Rogeberg et al., 2016)

Random effects: **OR 1.36 (1.15-1.61)**

Meta-regression: **OR 1.22 (1.1-1.36)**
NHTSA Crash Risk Study (Compton and Berning, 2015)

- First large scale U.S. study to include drugs other than alcohol
- 3,000 crash-involved and 6,000 control drivers in Virginia Beach, VA
- 24h/7 days per week response to crashes over 20 month period
- Match crashes by visiting site one week later, same time of day
- THC+ in blood

Unadjusted OR = 1.25
Adjusted OR = 1.05
Low substance use prevalence: ~7% drivers were THC+;
National Roadside Survey found 12.6% with THC

Adjusted Odds Ratio Between Drug Class Use and Crash Risk

![Graph showing adjusted odds ratio between drug class use and crash risk.](image)

**Adjusted Odds Ratio**

- ETOH + No Drug
- ETOH + Drug
- Sedatives
- Narcotic Analgesics
- THC (Marijuana)
- Illegal Drugs
- Antidepressants
- Legal Drugs
- Stimulants

**Odds Ratio**

*** = p < .0001
Car Following – Coherence Reduced by MJ*  (*ability to adjust to movement of car ahead of you)  
30 minutes Post-Smoking in CMCR study

Paired t-test THC+  
T1 vs T5  p = .97  
T1 vs T4  p = .80

![Graph showing coherence over time for Placebo and THC+ groups with statistical significance markers.](image)
Relationship Between Car Following Coherence and Whole Blood THC Levels Immediately Post-Smoking THC containing cannabis
Proportion of those receiving THC containing cannabis saying they would drive in their current state

- 30m: 48%
- 1h 30m: 69%
- 3h 30m: 90%
- 4h 30m: 94%
Self-perception vs. Performance

Perceived impairment

Reduced performance

Time
Cannabis blood levels/Breath alcohol level and simulator swerving

Hartman et al., 2015

% Increase in Swerving Relative to Baseline

THC ug/L - Breath Alcohol Level

THC Only  Alcohol Only  Combined

Hartman et al., 2015
Summary of current status of Medicinal Cannabis/Cannabinoid Modulators

- Smoked/vaporized cannabis, and extracts containing THC/CBD mix probably efficacious in neuropathic pain and spasticity from MS
- Possible efficacy in sleep disorders treatment
- Synthetic THC-like molecules efficacious in appetite stimulation and control of nausea
- Potential utility of other synthetic CB1 agonists not yet established
- CB1 antagonists, partial agonists may be useful in appetite suppression, but adverse psychiatric effects have been problematic
- Cannabidiol showing initial promise in treatment of anxiety, psychosis, and intractable epilepsy (e.g., FDA approved Epidiolex for seizures in Dravet; Lennox Gastaud; Tuberous Sclerosis)
- FAAH inhibitors promising in animal models of chronic pain
- Anti-inflammatory actions of cannabinoids deserve further exploration
Once we clear the smoke:
Examples of future research directions on medicinal cannabis

- Studies to address how patient diversity affects treatment response and vulnerability to adverse effects
  - Sex; Age; prior experience with cannabis; co-occurring conditions eg., psychiatric; non cannabis substance disorders; medical, eg., heart disease; liver disease

- Studies on differential effectiveness, adverse effects, of various delivery systems
  - eg., smoked; other inhalational; oral; transdermal; oral-mucosal; suppositories

- Studies on specific cannabinoids
  - eg., THC, CBD, their combination. Other cannabinoids and terpines?

- Studies on synergistic or sparing effects
  - Reduce or replace opioids, benzodiazepines, or other medications?

- Studies on dosing:
  - eg., are therapeutic [such as analgesic] effects gained at lower doses than psychoactive? Effects of cannabinoid combinations
Acknowledgements

Much of the Data Presented was with thanks to all our Study Volunteers and to Collaborating Investigators and Sponsors

Center for Medicinal Cannabis Research
Igor Grant, MD Director

- **Co-Directors**
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  Thomas D. Marcotte, PhD

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William Perry, PhD
Veena Ranganath, MD
Gabe Silva, PhD
Doris Trauner, MD

CMCR Funding Sources
State of California
Wholistic Research & Education Foundation
Krupp Endowed Fund
NIH NIDA
Essential Tremor Foundation
Medical Cannabis

Thank you!

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