Cannabis and its derivatives

Courtesy D. Piomelli, UCI
Cannabis: not a new medicine
Main Events that Reawakened Interest in Medicinal Cannabis in the 1990s

- Persistent anecdotal reports of benefits
- Political shifts favoring medicinal access (in USA 23 states now provide for some measure of access)
- Discovery of the endocannabinoid system
  - CB1 and CB2 receptors
  - 2-arachidonoylglycerol (2-AG: Sugiura, et al., Mechoulam et al., 1995), 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)
Distribution of CB1 Receptors

Green shading indicates distribution of cannabinoid receptors in the body
- CNS
- Intestine
- Liver
Distribution of CB1 Receptors

- **cerebral cortex**: decision making, cognition, & emotional behavior
- **caudate nucleus**: learning & memory system
- **putamen**: regulate movements & influence various types of learning
- **globus pallidus**: regulate voluntary movements
- **amygdala**: responsible for anxiety & stress, emotion & fear, pain
- **hypothalamus**: body temperature, feeding, neuroendocrine function
- **hippocampus**: memory & learning
- **substantia nigra**: important role in reward, addiction, & movement
- **cerebellum**: motor control & coordination
- **dorsal vagal complex**: emesis
The endogenous cannabinoids

Anandamide

Virodhamine

N-arachidonoyldopamine

2-Arachidonoylglycerol

Noladin ether

“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)
Marijuana Compounds

+ 80 cannabinoids

The NIH Workshop on the Medical Utility of Marijuana (1997) and the Institute of Medicine (1999), following thorough review, identified medical conditions warranting further research regarding the possible therapeutic effects of cannabis.

- Appetite Stimulation
- Nausea and Vomiting
- Analgesia
- Neurological and Movement Disorders
University of California Center for Medicinal Cannabis Research (CMCR)

Igor Grant, M.D.
Director

J. Hampton Atkinson, MD & Tom Marcotte, PhD, Co-Directors
Barth Wilsey, MD, Ron Ellis, MD, PhD, Mark Wallace, MD, Robert Fitzgerald, PhD, Investigators; Ben Gouaux and Jennifer Marquie Beck, Senior Staff

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California Events Leading To CMCR

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
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<tbody>
<tr>
<td>November 1996:</td>
<td>California Prop 215 passes: Compassionate Use Act</td>
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<tr>
<td>August 2000:</td>
<td>Center for Medicinal Cannabis Research established at the University of California.</td>
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<tr>
<td>September 2003:</td>
<td>Amendment to Medical Marijuana Research Act of 1999, sunset restrictions removed. (SB 295)</td>
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</tbody>
</table>
time from submission of CMCR approved study to state and federal regulators to study initiation was approx. 1 year (range 6-18 months)
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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</thead>
<tbody>
<tr>
<td>UCSD 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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<tr>
<td>UCSF 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>UCSD Ronald Ellis</td>
<td>HIV Neuropathy</td>
<td>Crossover RCT</td>
<td>28</td>
<td>0%, 1-8%</td>
<td>+</td>
</tr>
<tr>
<td>UCD Barth Wilsey</td>
<td>Neuropathic Pain, Experimental Pain</td>
<td>Crossover RCT</td>
<td>33</td>
<td>0%, 3.5%, 7%</td>
<td>+</td>
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<tr>
<td>UCD Barth Wilsey</td>
<td>Neuropathic Pain</td>
<td>Crossover RCT</td>
<td>39</td>
<td>0%, 1.29%, 3.53% (Vaporized)</td>
<td>+</td>
</tr>
<tr>
<td>UCSD Jody Corey-Bloom</td>
<td>MS Spasticity</td>
<td>Crossover RCT</td>
<td>30</td>
<td>0%, 4%</td>
<td>+</td>
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<tr>
<td>UCSD 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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</tbody>
</table>
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

$$\text{NNT} = \frac{1}{0.30} = 3.3$$
Common Analgesics for Neuropathic Pain

Number Needed to Treat

- 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.*
Ashworth spasticity scores before and after active and placebo cannabis administration. Active treatment reduced Ashworth Total Scores by an average of 2.7 points more than placebo (p<0.0001).

Source: Corey-Bloom, et al. (2012) CMAJ 184(10); 1143-1150.
Summary of CMCR Studies on Smoked Cannabis

- Data from CMCR placebo controlled, limited scale studies of smoked cannabis indicate positive response in neuropathic pain with effect sizes similar to other agents.
- One CMCR study also found smoked cannabis reduced spasticity in MS patients.
- Side effects were generally mild, with commonest being subjective high, fatigue, and tachycardia.
- Neurocognitive testing revealed small reversible decrements during active treatment; comparable to effects of benzodiazepines, and antispasm, antiepileptic drugs for neuropathic pain and spasm.
- Other side effects were sedation, dizziness, cough, throat irritation; all reversible and none necessitating discontinuation.
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
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%

## Studies on medicinal cannabis effects: Whiting et al (2015) meta-analysis

<table>
<thead>
<tr>
<th># RCTs</th>
<th>Condition</th>
<th># Reports</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>Chronic Pain</td>
<td>63</td>
<td>2454</td>
</tr>
<tr>
<td>28</td>
<td>Nausea and vomiting due to chemotherapy</td>
<td>37</td>
<td>1772</td>
</tr>
<tr>
<td></td>
<td>Spasticity due to multiple sclerosis/paraplegia</td>
<td>33</td>
<td>2280</td>
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<tr>
<td>14</td>
<td>HIV/AIDS</td>
<td>4</td>
<td>255</td>
</tr>
<tr>
<td>2</td>
<td>Sleep Disorder</td>
<td>5</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>Psychosis</td>
<td>9</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>Tourette syndrome</td>
<td>7</td>
<td>36</td>
</tr>
<tr>
<td>1</td>
<td>Anxiety disorder</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>1</td>
<td>Glaucoma</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>0</td>
<td>Depression</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Meta-Analysis

- moderate-quality evidence to support the use of cannabinoids in:
  - chronic pain
  - spasticity
- low-quality evidence suggesting that cannabinoids were associated with improvements in:
  - nausea and vomiting due to chemotherapy
  - weight gain in HIV infection
  - sleep disorders
  - Tourette syndrome

Other current or potential cannabinoid modulators

- **Agonists**
  - THC/CBD plant extract, eg., (Nabiximols)
  - Synthetic THC (Dronabinol [Marinol] & analogs]: Nabilone [Cesamet]; selective CB1 or CB2 agonists)

- **Antagonists, partial agonists**
  - (Rimonabant, Taranabant, etc)

- **Modifiers of endocannabinoid metabolism**
  - Fatty Acid Amide Hydrolase (FAAH) inhibitors; possibly monoglyceride lipase (MGL) inhibitors
Dronabinol for Appetite Stimulation

Mean change in appetite from baseline, evaluable patients.

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.

Cannabidiol - CBD

- Natural component of the Cannabis plant
- Constitutes up to 40% of marijuana extracts
- Devoid of typical psychological effects of THC
- Evidence for:
  - Anti-inflammatory
  - Analgesia
  - Anti-nausea
  - Hypnotic and sedative
  - Antipsychotic
  - Anticonvulsive
  - Neuro-protective
  - Anxiolytic
  - Others

- Antagonism of THC when both contents are administered concomitantly? FAAH inhibition?
## Cannabidiol: Human Models of Anxiety

<table>
<thead>
<tr>
<th>Study</th>
<th>Model</th>
<th>Anxiolytic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Humans</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zuardi et al. (1982)</td>
<td>Decreased STAI scores elevation induced by THC (healthy volunteers)</td>
<td>+</td>
</tr>
<tr>
<td>Zuardi et al. (1993)</td>
<td>Decreased VAS factor anxiety scores after public speaking (healthy volunteers)</td>
<td>+</td>
</tr>
<tr>
<td>Crippa et al. (2004)</td>
<td>Decreased VAS factor anxiety scores before SPECT procedure (healthy volunteers)</td>
<td>+</td>
</tr>
<tr>
<td>Fusar-Poli et al. (2009)</td>
<td>Decreased skin conductance fluctuation in task with fearful face during an fMRI procedure (healthy volunteers)</td>
<td>+</td>
</tr>
<tr>
<td>Crippa et al. (2011)</td>
<td>Decreased VAS factor anxiety scores before SPECT procedure (Social Phobic patients)</td>
<td>+</td>
</tr>
<tr>
<td>Bergamaschi et al. (2011)</td>
<td>Decreased VAS factor anxiety scores after public speaking (Social Phobic patients)</td>
<td>+</td>
</tr>
</tbody>
</table>

Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil
Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients

Mateus M Bergamaschi¹,²,³, Regina Helena Costa Queiroz²,³, Marcos Hortes Nishihara Chagas¹,³, Danielle Chaves Gomes de Oliveira¹,³, Bruno Spinosa De Martinis³,⁴, Flávio Kapczinski³,⁵, João Quevedo³,⁶, Rafael Roesler³,⁷, Nadja Schröder³,⁸, Antonio E Nardi³,⁹, Rocío Martín-Santos³,¹⁰, Jaime Eduardo Cecilio Hallak¹,³, Antonio Waldo Zuardi¹,³ and José Alexandre S Crippa*,¹,³

Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil
# Cannabidiol: Seizure Reduction in Epilepsy

<table>
<thead>
<tr>
<th>STUDY</th>
<th>MODEL</th>
<th>EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human</strong></td>
<td>N=137 children Dravet or Lennox Gastaud. Epidiolex, a CBD extract</td>
<td>+</td>
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<tr>
<td>Devinsky et al., 2015</td>
<td></td>
<td></td>
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<tr>
<td>Porter, et al. (2013)</td>
<td>N=19, children with treatment resistant epilepsy, survey results</td>
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<td>Trembly, et al. (1990)</td>
<td>N=12, 300mg cannabidiol/placebo</td>
<td>-</td>
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<tr>
<td>Ames, et al. (1985)</td>
<td>N=12, uncontrolled seizures, 200-300mg cannabidiol/placebo daily</td>
<td>-</td>
</tr>
<tr>
<td>Cunha, et al. (1980)</td>
<td>N=15, temporal lobe epilepsy, 200-300mg cannabidiol/placebo daily</td>
<td>+</td>
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<tr>
<td>Mechoulam, et al. (1978)</td>
<td>N=9, temporal lobe epilepsy, 200mg cannabidiol/placebo</td>
<td>+</td>
</tr>
<tr>
<td><strong>Pre-Clinical</strong></td>
<td>N=12, uncontrolled seizures, 200-300mg cannabidiol/placebo daily</td>
<td>-</td>
</tr>
<tr>
<td>Consroe, et al (1982)</td>
<td>Seizures induced by strychnine sulphate</td>
<td>-</td>
</tr>
</tbody>
</table>

Role for cannabinoids in schizophrenia treatment? Some evidence for cannabinoid involvement

- Heavy MJ use associated with increased risk of psychosis in some studies; THC itself can produce acute psychosis
- PCP administration (animal model of psychosis) associated with regional brain increase in 2 AG
- Human PET studies show increase in CB1 binding in various brain regions in untreated schizophrenia
- Serum/CSF anandamide increased during onset of psychotic symptoms, but not in heavy MJ users
- Higher CSF anandamide associated with less likely transition to psychosis in “high risk” cases
- In psychosis cases treated with cannabidiol, improvement in negative symptoms associated with greater CSF anandamide rise
Cannabidiol improves positive and negative symptoms of schizophrenia:
(42 cases randomized to receive 800 mg/d cannabidiol or amisulpride)

Compared to atypical antipsychotic amisulpiride, cannabidiol does not worsen extrapyramidal symptoms, and is not associated with weight gain or elevated prolactin.

Cannabis Induces a Clinical Response in Patients With Crohn’s Disease

500mg cannabis (23% THC) x2 daily
8 weeks treatment, 2 weeks washout

Smoked Cannabis Treatment for Motor and Non–Motor Symptoms of Parkinson Disease

Pre- and Post-treatment motor UPDRS score in 22 patients with and without response fluctuations 30 minutes after smoking 500mg cannabis.

FAAH inhibitors as therapeutic agents?
Peripheral FAAH inhibitor URB937 efficacious in animal model of post-surgical pain

Oral dosing
Strong, prolonged effect on pain

More effective and long-lasting than NSAIDs (oral) or opiates (ip)

Courtesy D. Piomelli, personal communication
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
- Very early data on possible efficacy of cannabis in Crohn’s Disease, Parkinson’s. Confirmation needed.
- 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 there are case reports on benefits for intractable epilepsy (eg., Dravet; Lennox Gastaut Syndromes)
- FAAH inhibitors promising in animal models of chronic pain
- Anti-inflammatory actions of cannabinoids deserve further exploration
How do we move forward? Let’s clear away the smoke and get past the heat and into the scientific light!

- We need to separate out discourse on medicinal cannabis from that of broader social policy on recreational use [as we have done with other potentially abusable substances]
- We need serious larger scale clinical trials on cannabis, administered via several routes, and specific constituents, plus their combinations.
- Governments are the logical sponsors of such trials, as there is not an immediate incentive for pharma to be involved. Tax dollars collected from cannabis sales can support such studies, which should also focus on longer term benefits, and possible individual toxicity, and broader social harm.
- In the USA and other jurisdictions regulatory authorities need to “re-schedule” cannabis away from the most restrictive schedule, recognizing that harm potential is modest, and there are likely medical benefits. This will facilitate medical research
- If cannabis is to be used as a medicine, it needs to be capable of MD prescription, in accordance with agreed protocols, and subject to availability from trusted sources that confirm potency and purity, and regulated dispensing [eg., pharmacies; regulated dispensaries]
Marijuana as Medicine: Can we see past the smoke?

Thank you!

Igor Grant, M.D.
Director

J. Hampton Atkinson, MD & Tom Marcotte, PhD, Co-Directors
Barth Wilsey, MD, Ron Ellis, MD, PhD, Mark Wallace, MD, Robert Fitzgerald, PhD, Investigators; Ben Gouaux and Jennifer Marquie Beck, Senior Staff

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Terpene phenolic heterocyclic structures of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Red portions identify basic terpene (left) and phenol (right) backbones.

Schematic of a GABAergic synapse modulated by CB1 receptors. The perisynaptic location of CB1 receptors (A) is depicted. GABA (E) stimulates post-synaptic GABA receptors (F). Post synaptic changes induce metabolism of membrane derived phospholipids (G) leading to formation of endocannabinoid (H). The latter diffuses back stimulating the perisynaptic CB1 receptor (A). This in turn modulates neurotransmitter release from presynaptic vesicles (D) via G-protein coupled (B) influence on Ca++ channels (C).

Chemical structures of the two major endocannabinoids: N-arachidonyl ethanolamide (AEA; “anandamide”) and 2 arachidonoylglycerol (2AG). Similarity to arachidonic acid and arachidonic acid metabolites is apparent.

Potential toxicities of cannabinoid preparations

**General toxicities**

- Tachycardia
- Pulmonary toxicity (inhaled formulation)
- Pulmonary infection
  - Inhalation of associated microorganisms/fungi
- Immune suppression
  - Suppresses macrophages, T-lymphocyte
  - Increased interleukin I release
- Associated intake of pesticides/byproducts

Potential toxicities of cannabinoid preparations

Neurologic and neuropsychiatric toxicities

Memory impairment
- Short and long term

Impaired executive functions
- ↓ concentration, judgment, attention span, motivation, problem solving, reaction time

Impaired motor function
- ↓ coordination

Impairment of neural plasticity

Neuropsychiatric

- Anxiety, panic attacks
- Psychosis
  - ? With or without predisposition
- Mania, manic episodes
  - ↑ cycling in bipolar
- Depression
- "Addiction”/dependence
  - "gateway drug”