Cannabis and its derivatives

Marijuana

Hashish

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)
States With Medical Marijuana Laws; States Where Cannabis is Legal

Sources: Politico; Reuters. Courtesy Ziva Cooper; Picture: Business Insider
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

Isolation, structure and partial synthesis of an active constituent of hashish.
Potential Medicinal Uses of Cannabis: NIH & IOM Reviews in late 90s

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

www.cmcr.ucsd.edu
California Events Leading To CMCR

November 1996: California Prop 215 passes: Compassionate Use Act


August 2000: Center for Medicinal Cannabis Research established at the University of California.

September 2003: Amendment to Medical Marijuana Research Act of 1999, sunset restrictions removed. (SB 295)
time from submission of CMCR approved study to state and federal regulators to study initiation was approx. 1 year (range 6-18 months)
Study Locations

UC-Davis
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.

<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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<td>UCSF</td>
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<td>Parallel Groups RCT</td>
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<td>UCD</td>
<td>Neuropathic Pain, Experimental Pain</td>
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<td>UCD</td>
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<td>39</td>
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</table>
How effective is cannabis relative to other pain medications? Number-Needed-to-Treat

- Number-Needed-to-Treat (NNT) = \( \frac{1}{\text{Proportion improved in experimental condition} - \text{Proportion improved on placebo}} \)

- 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.
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.
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

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
Mean plasma concentrations of Δ9-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH) following administration smoked cannabis vs. oral dronabinol.

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
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.

Current or potential cannabinoid modulators that may be administered orally

- **Agonists**
  - Cannabis itself
  - 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
Other Cannabinoids: Cannabidiol

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

Cannabidiol actions do not seem to involve endocannabinoid system

No psychoactive effect

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
- 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
# Cannabidiol: Seizure Reduction in Epilepsy

<table>
<thead>
<tr>
<th>STUDY</th>
<th>MODEL</th>
<th>EFFECT</th>
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<tbody>
<tr>
<td><strong>Human</strong></td>
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<tr>
<td>Devinsky et al., 2015</td>
<td>N=137 children Dravet or Lennox Gataud. Epidiolex, a CBD extract</td>
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<td>Ames, et al. (1985)</td>
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<td>Cunha, et al. (1980)</td>
<td>N=15, temporal lobe epilepsy, 200-300mg cannabidiol/placebo daily</td>
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<td>Mechoulam, et al. (1978)</td>
<td>N=9, temporal lobe epilepsy, 200mg cannabidiol/placebo</td>
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<td><strong>Pre-Clinical</strong></td>
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<td>isonicotinic acid hydrazide, electroshock induced seizures</td>
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<tr>
<td>Consroe, et al (1982)</td>
<td>Seizures induced by strychnine sulphate</td>
<td>-</td>
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</tbody>
</table>

Cannabidiol (CBD) Significantly Reduces Drop Seizure Frequency in Lennox-Gastaut Syndrome (LGS)
Proportion of patients achieving 50% or greater reduction in episodes

- Thiele AE et al. The American Epilepsy Society Annual Meeting; Houston, TX; December 2–6, 2016.
Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients

Neuropsychopharmacology (2011), 1–8
© 2011 American College of Neuropsychopharmacology. All rights reserved 0893-133X/11 $32.00

Mateus M Bergamaschi¹,²,³, Regina Helena Costa Queiroz²,³, Marcos Hortes Nisihara 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, Rocio Martín-Santos³,¹⁰, Jaime Eduardo Cecílio 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
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.

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 (eg., Dravet; Lennox Gastaud Syndromes: FDA panel recommends Epidiolex approval 4/19/18)
- FAAH inhibitors promising in animal models of chronic pain
- Anti-inflammatory actions of cannabinoids deserve further exploration
Medical Cannabis: Potential Public Health Benefits

- Decreased opioid analgesic overdose deaths
  - Mean 25% decrease in states with medical cannabis
    (Bachhuber, et al., *JAMA Int Med*, 2014)
- Decreased opioid analgesic misuse
  - Decreased treatment admissions for prescription opioid misuse
- Decreased obesity
  - Associated with 2-6% decreased probability of obesity
- Decreased alcohol use
  - Mixed findings

Courtesy David Gorelick, MD
Medical Cannabis: Potential Public Health Harms

- Increased cannabis use
  - Found in some, but not all, epidemiological analyses

- Increased incidence of cannabis use disorders
  - Small increase in recent epidemiological analysis (Hasin et al., *JAMA Psychiatry*, 2017)

- Increased alcohol use
  - Some evidence for both increased and decreased use (substitution)

- Increased cannabis-associated motor vehicle accidents

- Increased unintended cannabis overdoses
  - In Colorado, especially among children (e.g., Davis et al., *JAMA Psychiatry*, 2017)

- Increased crime around cannabis dispensaries
  - Only in immediate vicinity (Long Beach, CA study)

Courtesy David Gorelick, MD
How do we move forward? In most countries, including the USA, it isn’t that easy

- We need to separate out discourse on medicinal cannabis from that of broader social policy on recreational use [as we have done with other abusable drugs]
- We need both proof of principle and larger scale clinical trials on cannabis, administered via several routes, and specific constituents, plus their combinations. Consider effects of age, sex, comorbidities, other medications
- Tax dollars collected from cannabis sales can support such studies, which should also focus on longer term benefits, toxicity, and broader social effects.
- In the USA and other jurisdictions regulatory authorities need to “re-schedule” cannabis away from the most restrictive designation, recognizing that harm potential is modest, and there are medical benefits. This will facilitate medical research. Example: CBD, which is non psychoactive, is still Schedule 1 and practically unavailable for broader medical research
- In the USA the Federal Government needs to empower States to license producers for medical research to make available a diversity of products in a timely manner.
- If cannabis is to be used as a medicine, it needs to be capable of physician 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].
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
Medicinal Cannabis

Thank you!

Igor Grant, M.D.
Director

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