The Promise, and Challenge, of Cannabis and Cannabinoids as Medicine

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HIV Neurobehavioral Research Program
University of California, San Diego
Cannabis Legalization by State

Recreational: 11, D.C.  Medical: 33, D.C  Low THC/High CBD: 13
(Source: National Conference of State Legislatures)
Interest in Medicinal Cannabis Reawakened in the 1990s

- Persistent anecdotal reports of benefits (e.g., PWH)
- Discovery of the endocannabinoid system
- Political shifts favoring access to medicinal cannabis

Should Cannabis be Made Legal?

Pew Research Center, 2018
California Developments: Center for Medicinal Cannabis Research

1996  Compassionate Use Act
1999  Medical Marijuana Research Act
2000  CMCR established (California SB 847; Vasconcellos)
2016  Adult Use of Marijuana Act (Proposition 64)

*Ongoing CMCR funding*

**Mission**

- Facilitate high quality scientific studies
- Ascertain the safety and efficacy of cannabis and cannabinoid products
Cannabis Constituents

- **Cannabinoids** (> 100 cannabinoids)
  - Delta-9 THC: psychoactive; synthesized within the glandular trichomes in the flowers, leaves, and bracts of the female plant
  - CBD: non-intoxicating cannabinoid

- **Terpenoids**: aroma, modulate how cannabinoids interact with receptor, may act on serotonin, dopamine, etc.

- **Flavonoids**: color of plant, anti-oxidants, anti-inflammatory?
Two types of cannabinoid receptors (1980/90s)

- **CB1**
  - Primarily in the brain, intestine, liver
  - Responsible for psychoactive effects

- **CB2**
  - Immune cells
  - Reduces inflammation

Endocannabinoid System (ECS)

- Two key ECs have been identified (1990s)
  - Anandamide (AEA)
  - 2-arachidonylglycerol (2-AG)

- Synthesized on demand; disappear very quickly
- Like a “dimmer switch” (promoting homeostasis)
Cannabis: not a new medicine

One-Fourth Ounce Solid Extract
CANNABIS AMERICANA
(Cannabis sativa—American grown)
PHYSIOLOGICALLY TESTED
DOSE—1-5 to 1 grain

ONE-FOURTH POUND—SOLID EXTRACT
CANNABIS AMERICANA
PHYSIOLOGICALLY TESTED
(Cannabis sativa—American Grown)
Analgesic, Hypnotic, Spasmodic and powerful Narcotic
DOSE—1-5 to 1 grain

OCT 11 1913

ELI LILLY & CO., INDIANAPOLIS, U. S. A.
Guaranteed by Eli Lilly & Co., under Food and Drugs Act, June 30, 1906. Guaranty No. 87.
The Health Effects of Cannabis and Cannabinoids

- Cannabis and cannabinoid studies since 1999 IOM report
- Systematic reviews (since 2011) and high-quality primary research
- Human studies (no basic nonhuman research)

- **Substantial/conclusive evidence**
  - Chronic pain
  - Spasticity of multiple sclerosis
  - Control of nausea

- **Moderate evidence**
  - Improving sleep in those with chronic medical conditions (e.g., chronic pain, fibromyalgia, etc.)

- **Limited evidence**
  - Certain anxiety disorders and PTSD
  - Promoting appetite and weight gain

- **No or insufficient evidence**
  - Treatment of cancers, irritable bowel syndrome, epilepsy, movement disorders due to Huntington Disease or Parkinson Disease, schizophrenia
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.

Low and Medium Dose Demonstrated Equivalent Analgesia

Possible “Window” for Cannabis-Related Analgesia (Wallace et al., 2007)

- 15 healthy adults
- THC levels
  - Low (2%)
  - Medium (4%)
  - High (8%)
- Capsaicin (intradermal)
- 40 minutes post-dosing
- Pain measurements
  - Spontaneous pain (VASPI)
  - Brush
  - Hair (von Frey)
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)
Is cannabis anti-inflammatory and neuroprotective?
Impairment Rates

Naïve Infrequent 49.7%
Moderate 36.1%
Frequent 47.8%

Neurocognitive Impairment (NCI)

Heaton, Iudicello, Letendre
Biopsychosocial Predictors of SuperAging in PWH (Saloner et al., 2019)

- Probability of Superaging (vs. Normal for Age)
- Probability of Superaging (vs. Impaired for Age)

Predictor

- WRAT (per 1SD increase)
- Cannabis Use Disorder
- Age (per 1SD increase)
- BDI-II (per 1SD increase)
- Diabetes

Odds Ratio

0.20
0.50
1.00
2.00
4.00
Medicinal Cannabis Challenges
Research and Implementation

- Smoking as a delivery method
- DEA scheduling
- Access to different constituents
- Access to real-world cannabis
Challenges in Using Smoked Cannabis as Medicine

- 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

**Plasma THC**

**Expired CO**

STORZ & BICKEL GMBH & CO. KG
Medicinal Cannabis Challenges
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DEA Scheduling

I  No currently accepted medical use and high potential for abuse
    Heroin, LSD, Ecstasy

II High potential for abuse, potentially leading to dependence
    Vicodin, cocaine, methamphetamine, methadone, fentanyl, Adderall

III Moderate to low potential for physical and psychological dependence
    Tylenol with codeine, ketamine, anabolic steroids, testosterone

IV Low potential for abuse or dependence
    Xanax, Darvocet, Valium, Ativan, Ambien

V Lower abuse risk than IV, limited quantities of narcotics; (antidiarrheal, analgesic)
    Robitussin AC, Lomotil, Lyrica

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<thead>
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<th>II</th>
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</table>

- THC: Tetrahydrocannabinol
- CBD: Cannabidiol
- Synthetic: Synthetic compounds
- Plant: Botanical extracts
- Plant-based: Botanical preparations
- Hemp: Botanical extracts from hemp

- ✔: Available
- -: Not available

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**Center for Medicinal Cannabis Research**

University of California, San Diego
Farm Bill of 2018 – Hemp

FDA Stance

- FDA regulates products containing cannabis or cannabis-derived compounds
- Cannabis and cannabis-derived products... are considered new drugs or new animal drugs and must go through the FDA drug approval process
  » Both CBD and THC are active ingredients in FDA-approved drugs
  » Illegal to introduce drug ingredients like these into the food supply, or to market them as dietary supplements
- FDA Hearing: *Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds* (May 31, 2019)
  » 140 presentations
  » > 4,400 public submissions during public comment period
Medicinal Cannabis Challenges
Research and Implementation

- Smoking as a delivery method
- DEA scheduling
- Access to different constituents
- Access to real-world cannabis
DEA August 2019 Announcement
Increasing the Number of Cannabis Manufacturers

- NIDA/University of Mississippi is only legal source for plant (now non-hemp) material
- 2016: DEA announced expansion of entities permitted to grow cannabis
  » No feedback on applications (n = 33)
- DEA intends to propose regulations that would supersede the 2016 policy statement
- Growing cannabis that contains no more than 0.3 percent delta-9 THC on a dry weight basis, including cannabidiol (CBD), applicants no longer require DEA registration for that purpose
Medicinal Cannabis Challenges
Research and Implementation

- Smoking as a delivery method
- DEA scheduling
- Access to different constituents
- Access to real-world cannabis
Research Options:
Potential Medicinal Benefits

- Capsules
- Infused Drinks
- Ointments
- Tinctures
- Edibles
- Oils
Challenges in Assessing the Impact of Cannabis on Driving: Accessing Real World Cannabis or Similar Products

- Non-flower products are in wide use (edibles, drinks, wax, oils, concentrates)
- Unable to even analyze (THC levels, contaminants) what is currently in use in the community; violation of Federal law to even receive them
- Edibles: THC-infused food (baked goods [cookies], chocolates, gummies)
  - Pass through the liver (first-pass metabolism)
  - THC transformed to 11-hydroxy-THC (readily crosses blood-brain barrier)
  - Hour to 1.5 hours to feel full effect
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.

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<tr>
<th>Condition</th>
<th>Product</th>
<th>Funding</th>
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<tbody>
<tr>
<td>Induced Pain</td>
<td>NIDA THC</td>
<td>State of CA</td>
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<tr>
<td>Diabetic Neuropathy*</td>
<td>NIDA THC</td>
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<tr>
<td>HIV Neuropathy*</td>
<td>NIDA THC</td>
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<tr>
<td>Multiple Sclerosis Spasticity*</td>
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<td>HIV Neuropathy*</td>
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<td>NIDA THC</td>
<td>National Institutes of Health</td>
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## CMCR - New Studies (*Treatment trials*)

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<td>Migraine*</td>
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### CMCR Grants Program

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<td>Early Psychosis*</td>
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<td>Rheumatoid Arthritis*</td>
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<td>Anorexia Nervosa*</td>
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<tr>
<td>Alcohol Dependence</td>
<td>Plant-based CBD</td>
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</table>
Effect in Diverse/Vulnerable Populations
HIV and Aging

- Substantial changes in pharmacokinetics and pharmacodynamics
- Reduced hepatic drug clearance and renal elimination
- Increased body fat and decreased lean body mass
  » increase depot for cannabinoids and their metabolites
- Polypharmacy is common, but little is known about drug-drug interactions with cannabinoids
- Cardiovascular risks
- Pulmonary risks
- Cannabis Use Disorders
Medicinal Cannabis Research

- Hypothetically, cannabis’ potential anti-inflammatory and neuroprotective qualities could provide some cognitive benefit to PWH
- Need for greater diversity: cannabinoids, terpenoids, and flavonoids
  - Synthesis, biosynthesis options increasing; ability to produce minor cannabinoids
  - Importance, or not, of an “entourage effect”
- The lack of access to products in widespread use is significantly limiting
  - Impact of dosing/administration methods - Vaping, dabbing, higher THC content flower
- The effectiveness and adverse effects associate with various delivery systems (e.g., inhaled, oral, transdermal); controlled dosing
- Larger scale, longer-term clinical trials assessing benefits, and possible toxicities
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