The Medicinal Use of Cannabis

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Cannabis is... probably the most satisfactory remedy for the treatment of migraine headaches.

-- Dr. William Osler. Textbook of Medicine, 1892 - 1915
Marijuana has... a high potential for abuse and no accepted medical value.

-- Controlled Substance Act, 1970 - 2017
Outline

1. Terminology
2. Biology
3. Medicinal Use
4. Preparations
5. Legal and Administrative
Categories of Cannabinoids

Phytocannabinoids
- Cannabis sativa plant: 104 cannabinoids; 545 total compounds

Endocannabinoids
- 4+ cannabinoids in human body (endogenous ligands)

Synthetic cannabinoids
- Multiple chemically synthesized cannabinoids: pharmaceutical and recreational
# Cannabis Sativa Plant: Names

## Hemp
- Refers to the plant and its products
- Oldest term

## Marijuana
- Refers to both plant and drug
- Relatively new slang term

## Cannabis
- Refers to both plant and drug
- DSM-5: “most appropriate scientific term”
Cannabis Sativa: A Unique Plant

• Source of 3 important types of products
  1. Fiber (fabric, rope)
  2. Food (seed, oil)
  3. Psychoactive substances
     • Used for religious rituals, medicine, recreation

• Controversy about whether Cannabis *Indica* exists as a separate subspecies
Cannabis Sativa: Ingredients

- Tetrahydrocannabinol (THC)
  - Primary, but not only, psychoactive ingredient of plant

- Cannabidiol (CBD)
  - No rewarding, euphorigenic effect
    - Counteracts psychoactive effect of THC

- THC and CBD are inversely proportional in cannabis plant
  - Strains developed based on goal of use
2. BIOLOGY
Modern Timeline

1940. Cannabidiol (CBD) isolated from plant
1964. THC isolated from plant
1981. CBD anticonvulsant effect demonstrated
1985. Synthetic THC approved by FDA
1988. CB1 receptor identified
1992. Endogenous anandamide (AEA)
1993. CB2 receptor identified
1995. Endogenous 2-arachidonoyl glycerol
• 86 y.o. Israeli chemist, still professionally active
• Identified THC as the primary psychoactive ingredient in cannabis
• Discovered the endocannabinoid system
• “The Scientist”: YouTube documentary about his discoveries
  – https://www.youtube.com/watch?v=csbJnBKqwlw
Endocannabinoid System: Helps Regulate Multiple Systems

- Pain
- Immunity
- Inflammation
- Movement
- Bone density
- Tumor surveillance
- Appetite
- Stress
- Mood
Endocannabinoid Receptors

• **CB1**
  - Most common receptor in CNS
    - Responsible for psychoactive effects
    - Absent in brain stem → no respiratory depression
  - Also in peripheral nerves and non-neuronal tissues

• **CB2**
  - Located in macrophages
  - Involved in immune system and anti-inflammatory activity
    - Exact functions unknown due to absence of good probes

• **Both inhibit synaptic transmission**
• **Other receptors not as well characterized**
Endocannabinoid Ligands

- Anandamide (AEA)
  - Partial agonist
  - CNS: Stress response. Periphery: pain
  - Metabolized by fatty acid amide hydrolase (FAAH)
- 2-arachidonoyl glycerol (2-AG)
  - Full agonist
  - Broadly expressed. “Workhorse”
  - Metabolized by mono-acyl-glycerol (MAGL)
- Ligand diversification: Both act on CB1 receptor but act differentially to modulate systems
Cellular Neurobiology

• **Neuromodulator (vs. neurotransmitter)**
  – Synthesized on demand rather than stored
  – Lipids derived from cell membranes, not proteins

• **Retrograde signaling**
  – Synthesized in post-synaptic cell and released into synaptic cleft
  – Binds to pre-synaptic CB1 receptor
  – Acts on pre-synaptic cell to inhibit release of both excitatory and inhibitory neurotransmitters

• **Interacts with opioid system**
Endocannabinoid System

- Pre-Synaptic Neurons
- Calcium Channel
- Neurotransmitter Vesicles
- Glutamate
- GABA
- Glutamate Receptor
- Metabotropic Glutamate Receptor
- Arachidonic Acid
- 2-AG
- G-Protein Complex
- CB₁
- THC
- Anandamide
- Arachidonic Acid
- Ethanolamine
- DAG
- DGL-a
- Pifx
3. MEDICINAL USE
Efficacy

• High quality evidence
  – Chemotherapy-induced nausea and vomiting
  – Appetite stimulation
  – Chronic pain, neuropathic (especially HIV/AIDS)
  – Spasticity of multiple sclerosis, spinal cord injury
  – Anticonvulsant (CBD for Dravet Syndrome)

• Low quality evidence
  – Anxiety, sleep disorders, PTSD

• Possible role in addiction treatment
  – Reduce cannabis withdrawal
  – CBD counteracts psychoactive effect of THC
  – CB1 blocker rimonabant withdrawn 2008
Cannabinoids and Pain

- Analgesic properties extensively documented and widely accepted in Western medical practice in 19th and early 20th Centuries
  - “Used for pain since beginning of recorded time.”
  - Prescribed to Queen Victoria for pain
  - Especially for neuropathic and inflammatory pain
- Do not induce tolerance
- Interact with opioid system and may allow reduced doses of opioids
  - CB1 receptors: 10 x more in CNS than mu-opioid receptors, especially in pain areas
Cannabinoids and Pain: Review of RCTs
(Agarwal)

- 38 studies, mostly outside of U.S.
- Preparations: synthetic, extracted, herbal
- Routes: oral, oro-mucosal, smoked, topical
- Results: 71% found statistically significant pain relief
  - Modestly effective
  - Safe and well tolerated
Cannabinoids and Pain: Review of RCTs

Indications

- Neuropathic pain
- Fibromyalgia
- Rheumatoid arthritis
- HIV neuropathy
- No reduction in viral load or CD4 cell count

Advantages

- Minimal tolerance
- No toxic overdoses or end organ failure
- Enhances analgesic effect of opioids
# Cannabinoids and Pain: Review of RCTs

## Adverse Effects
- Vast majority are not serious
- No withdrawals from study versus 33% for opioids
- Cognitive impairment
- Intoxication
  - Reduced by co-administration of CBD
- Addiction and withdrawal

## Contraindications
- History of Cannabis Use Disorder
- Use cautiously if history of psychosis
Safety

- No overdose deaths
  - Absence of CB receptors in brainstem
- Intoxication
  - Impaired driving
    - Especially if mixed with alcohol
  - Delayed effect
- Addictive potential
  - “Gateway hypothesis”
- Cognitive deficits resulting from heavy use before age 18
- Fetal development
  - Negative effect on cognitive functioning in children
- Association with psychosis
  - Causation possible
Percentage of People Addicted After Using A Substance

- Nicotine: 32%
- Heroin: 23%
- Cocaine: 17%
- Alcohol: 15%
- Stimulants: 11%
- Cannabis: 9%
- Sedatives: 9%
- Psychedelics: 5%
- Inhalants: 4%
4. PREPARATIONS
Pharmaceutical: Synthetic, Oral

• Dronabinol (Marinol, Syndros)
  – Synthetic THC isomer
  – Schedule III
  – Indications
    • Anti-emetic for cancer chemotherapy when other medications have failed
    • Anorexia from AIDS

• Nabilone (Cesamet)
  – Analogue of dronabinol
  – Schedule II
  – Indication
    • Anti-emetic for cancer chemotherapy when other medications have failed
Pharmaceutical: Plant Extract

• “Entourage Effect”
• FDA has approval path for botanical medication
• Sativex (1:1 ratio of THC/CBD)
  – Oro-mucosal spray (2.7 mg THC/2.5 mg CBD)
  – Approved in 28 countries for spasticity from multiple sclerosis, neuropathic pain, cancer pain
  – U.S.: Phase III clinical trials, fast tracked by FDA in April, 2014
• Epidiolex (cannabidiol)
  – Purified liquid extract
  – Anticonvulsant for Dravet syndrome
  – Orphan Drug Status from FDA, pre-IND
## Development of Parallel Systems

<table>
<thead>
<tr>
<th></th>
<th><strong>“Medical Marijuana”</strong></th>
<th><strong>Pharmaceutical Cannabinoids</strong></th>
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<tbody>
<tr>
<td><strong>Form</strong></td>
<td>Raw plant or extracts</td>
<td>Synthesized or extracted by government standards</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>Smoked, oral, topical</td>
<td>Oral (capsule or spray)</td>
</tr>
<tr>
<td><strong>DEA Class</strong></td>
<td>Schedule I</td>
<td>Schedule II, III</td>
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<tr>
<td><strong>Physician Role</strong></td>
<td>Recommend</td>
<td>Prescribe</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>“Artisanal” growers and dispensaries</td>
<td>Pharmaceutical companies and pharmacies</td>
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Non-Pharmaceutical Preparations

• Quality and standardization issues
  – Artisanal vs. scientific
  – Pesticides, contaminants
  – New emphasis on “product safety protocols”
    • Maryland has adopted American Herbal Products Association standards

• Production is evolving from home grown and co-ops to regulated businesses
  – Outdoor versus indoor (artificial vs. natural light)
Non-Pharmaceutical Preparations: European Example

- Whole-flower
- Varieties with standardized THC/CBD ratios
  - 22%/<1%
  - 14%/<1%
  - 7%/9%
  - <1%/9%
5. LEGAL AND ADMINISTRATIVE
Many Puzzles

1. Why was cannabis removed from clinical medicine without having the problems of over-prescription and overdoses experienced with opioid medications?

2. Why is the endocannabinoid system not taught in medical schools?

3. Why is cannabis the most difficult of the Schedule 1 substances to research?
Repetitious Process

1. Concern about widespread illegal use and uncertainty about facts
2. Appointment of high level government commission or scientific committee
   - Conclusion: “Cannabis is not without dangers, but penalties for use are disproportionate to the threat”
   - Recommend decriminalization
3. Opposition from law enforcement, politicians, some physicians
4. Sweeping, confident, disrespectful assertions by extremes on both sides
5. Stalemate with minimal or no legal changes
Commissions and Committees

- 1893-4, UK: Indian Hemp Drugs Commission
- 1929, U.S.: Panama Canal Zone Military Investigation
- 1939-44, U.S.: LaGuardia Report. NY Academy of Science
- 1968, UK: Baroness Wootton
- 1970, Canada: Le Dain Commission
- 1999, U.S.: Institute of Medicine
Long History of Medicinal Use

- 2700 BC. First documented use (China)
- Used for millennia in India, China, Egypt, Middle East
- Western medicine: mainstream use in 19th and early 20th Centuries
  - 1850 to 1942. Listed in U.S. Pharmacopoeia
    - Fluid extracts (not raw plant for inhalation)
    - Manufactured by major pharmaceutical companies
  - Included in major medical publications
    - William Osler’s textbook and others
De-Medicalization of Cannabis
(Harry Anslinger)

1937
Marijuana Tax Act
- Allowed medical use but imposed heavy administrative burdens
- Adopted despite AMA opposition
- Declared unconstitutional in 1969

1942
Removed from U.S. Pharmacopeia

1961
Included in UN Single Narcotics Convention

1970
Classified as Schedule 1 Substance in Controlled Drug Substances Act
1. High potential for abuse

2. No currently accepted use for treatment in the United States

3. Lack of accepted safety for use under medical supervision
"Since there is still a considerable void in our knowledge of the plant and effects of the active drug contained in it, our recommendation is that marijuana be retained within Schedule I at least until the completion of certain studies now underway to resolve the issue."

Dr. Roger O. Egeberg
Assistant Secretary of Health
August 14, 1970
**Simplified Legal Alternatives**

1. **Decriminalize**
   - Treat possession of small amounts as a civil offence or misdemeanor instead of a felony
     - Manage offenses with fines instead of incarceration
     - Intent: discourage use, prohibit distribution

2. **Legalize for recreational use**
   - Regulate and tax like alcohol and tobacco
   - Intent: eliminate black market, collect taxes
   - Opens door for commercial marketing

3. **Legalize for medical use**
Current Conflicted Legal Status

- Federal law: Use is illegal for any purpose
- Many state laws allow medical or recreational use
- The Supremacy Clause of U.S. Constitution:
  - State laws that actively impede or conflict with federal law are invalid
Medical Legalization History

• 1981. First bill introduced in US Congress (AIDS)
• 1996. California became first state to legalize
  – System flourished despite Federal raids
  – Drug czar threatened physicians with loss of DEA license if they recommended cannabis
  • 2002. Blocked by 9th Circuit. Supreme Court refused to hear appeal thus allowing ruling to stand
• 2005. Supreme Court allowed Federal government to intervene on users, growers, enterprises despite state law (Gonzales v. Raich)
  – Perpetuates gray area
• 2009. DOJ “Ogden Memo”: deprioritize CSA enforcement in states where medical cannabis is well regulated
• 2014. Rohrbacher-Farr Amendment (US House of Rep). Blocks DOJ from intervening
  – 2015. Court decision ordered DOJ to comply
• 2015. CARERS Act would eliminate gray zone
  – 2017. Passage is uncertain
• 2016. DEA reiterated refusal to reschedule
  – Will permit growers other than Univ of Mississippi
Summary of 2017 Status

• Medically legal in 28 states
  – 14 additional states permit cannabidiol oils
• Patchwork of state programs – no set of best practices
• Quality of substance from non-pharmaceutical sources is evolving
• For physicians
  – Legal gray zone has narrowed but persists
    • Physicians are protected from prosecution or loss of DEA license
  – Few clinical guidelines
Resulting Obstacles in U.S.

- **Access**
  - Single source for research grade
    - University of Mississippi farm, contracted by NIDA
    - Low THC concentration of research grade
    - Fall, 2016: DEA willing to allow other sources
  - 5 levels of approval (more than any other drug)
    - DEA – not FDA – has final authority

- **Organizational issues**
  - No government agency focused on beneficial uses

- **Discourages development of new pharmaceutical products**
Medical Cannabis in Maryland

• Law enacted 2013 and 2014, amended 2015
• Regulated by Maryland Medical Cannabis Commission
  – Final regulations issued October, 2015
• Process
  – Physicians must register
  – Producers and dispensaries must be licensed
  – Physician writes recommendation for patient
    • Any condition that is severe, for which other medical treatments have been ineffective, and if the symptoms “reasonably can be expected to be relieved” by the medical use of cannabis.
  – Patient obtains medication from dispensary
Current Status of Maryland Program

- Patients are not yet being registered
- 214 physicians registered as of February 2017
- Growers and processors licensees announced August, 2016
  - Challenges pending
- Updates and answers to FAQs at: mmcc.maryland.gov
What Are We Learning?

• Market forces join political forces to obscure scientific issues
  – Expansion or elimination of qualifying conditions
  – Importance of pricing to avoid gray market
• Most recommendations are made by a small subset of physicians
• Some de facto recreational use occurs
  – See increase in heavy use more than general use
  – No significant increase in use by youth so far
• Thorny issues remain to be resolved
  – Impaired driving
  – Positive urine screens at work
Summary

• Cannabis has medicinal value
  – Benefits and risks tend to be exaggerated
• Influence of law enforcement agencies has outweighed health agencies
• Political considerations have interfered with scientific evaluation and left physicians in a disadvantaged position
  – Beware of selective use of data to support particular positions
• Barriers to research and pharmaceutical development should be lowered
• NIH Cannabis Neuroscience Research Summit, March 22-23, 2016
• **Policy**
  – Harry Anslinger’s Congressional testimony: http://www.druglibrary.org/schaffer/hemp/taxact/anslng1.htm
Questions and Comments

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