The Science and Practice of Cannabinoid-Based Therapies

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Cannabinoids and Terpenes

- Cannabinoid is the generic term for the active constituents produced by strains of the cannabis plant (e.g., C. sativa)
- The Cannabis sativa herb ("marijuana") contains over 100 phytocannabinoid compounds
- Δ⁹-tetrahydrocannabinol (Δ⁹-THC) and Cannabidiol (CBD) most common
- Hemp is cannabis that contain less than 0.3% Δ⁹-THC and high concentration of CBD
- Synthetic cannabinoids (e.g., dronabinol; nabilone)
- Terpenes are produced in cannabis trichome and are responsible for the plant’s characteristic fragrance

History of Cannabis and Endocannabinoid Discovery

- 10000 BP First evidence of Cannabis exploitation
- ~6000 BP Evidence of Cannabis cultivation in Matsugasaki and Torihama sites
- 4650 BP First record of medical cannabis use in China
- 2750 BP Described in foundational Ayurvedic medicine text
- 25 Analogic properties of Cannabis, documented in China for surgical procedures
- 1484 Pope Innocent VIII condemned Cannabis “magic” practices
- 1930s Modern history of medical Cannabis begins ("Golden Age" of Cannabis)
- 1937 Marijuana Tax Act
- 1964 Mechoulam identifies Δ⁹-THC primary psychoactive component of the cannabis plant

History of Cannabis and Endocannabinoid Discovery (continued)

- 1968 University of Mississippi federal contract to cultivate marijuana for research
- 1970 Controlled Substances Act of 1970 (CSA) classified cannabis as schedule 1
- 1980s Devane & Howlett hypothesize existence of CB receptors - Δ⁹-THC-like molecules in body
- 1988 Herkenham mapped CB1 sites in the rat brain - molecular cloning of the first cannabinoid receptor gene
- 1992 Devane et. al. discovered the endogenous cannabinOID anandamide
- 1993 Munro cloned CB2 Receptor
- 1996 Croci et al. discovered fatty acid amid hydrolase (FAAH)
- 2000s Expansion of states legalization; growing interest in cannabinoids therapeutic potential
- 2018 FDA approved Epidiolex®, plant-derived CBD product, for childhood-onset epilepsies
- 2019 NCCIH funds 9 grants to investigate the potential pain-relieving properties of minor cannabinoids and terpenes.
- 2020 NCCIH reaffirms its commitment to supporting cannabinoid and terpene research for therapeutic potential

Mechanism of Action of Cannabinoids

Endocannabinoids are produced on demand. They travel back to the transmitting neuron to dampen further activity.

Cannabinoid (CB1) Receptors Are Located Throughout the Brain

- Brain Development
- Memory & Cognition
- Movement Coordination
- Pain Regulation & Analgesia
- Immune Function
- Appetite
- Motivational Systems & Reward
Cannabinoid CB1 Receptors: Human Brain

Areas with high CB1 density include:
- Prefrontal cortex
- Occipital cortex
- Putamen
- Hippocampus
- Thalamus
- Cerebellum

PET images from 40 to 80 min after injection of [11C]MePPEP


Cannabinoid Receptors are also Located Throughout the Body

Whole Body Distribution of CB1 Receptors [11C-MePPEP]

Distribution of CB2 Receptors [11C]-NE40

Terry et al., Eur J Nucl Med Mol Imaging, 2010

Ahmad et al., Mol Imaging Biol. 2013

Molecular Targets for Cannabidiol (CBD)

Molecular Targets for Cannabidiol (CBD)

Hille et al. Pharmacology & Therapeutics 133 (2012) 79-97

Bench To Bedside: Drug Development

Bench To Bedside: Drug Development

Form Research America: https://www.researchamerica.org/advocacy-action/issues-researchamerica-advocates/bench-bedside-drug-development-pipeline

“High Hopes Ride on Marijuana Painkillers Amid Opioid Crisis”

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#Health News June 23, 2017

http://www.reuters.com/article/us-marijuana-fda-idUSKBN19E1NU

Axim Biotechnologies, Inc., Nemus Bioscience, Inc., and Intec Pharma Ltd. have drugs in various stages of development

Plant Cannabinoids: Therapeutic Opportunities

Phytocannabinoids exert a wide range of pharmacological effects many of which are of potential therapeutic interest

Izzo, A.A., et al., Trends in Pharmacological Sciences Vol.30, No.10
Cannabinoid-based Medications


**EPIDIOLEX® (cannabidiol)**
100mg/ml Oral Solution
The First FDA-approved Plant-derived Cannabinoid Medicine

- Indicated for seizures; Lennox-Gastaut syndrome or Dravet syndrome
- 2.5 mg/kg PO BID initially; dose may increase to 5 mg/kg BID
- Adverse reactions: somnolence, decreased appetite, diarrhea, transaminase elevations, fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; and infections
- Subjective measures of Drug Liking and Take Drug Again within placebo range

**Sativex® (nabiximols in the US)**
100 microliter spray contains 2.7 mg THC and 2.5 mg CBD

- Indicated for multiple sclerosis (MS) to improve symptoms related to muscle stiffness ("spasticity"); is probability effective for reducing the number of bladder voids per day (ACN, 2014)
- Number of sprays each day depends on individual for best relief with the fewest unwanted effects
- Inadvisable to use the preparation during pregnancy or nursing
- 4 sprays 1X, no more liability for abuse than placebo; 8 -16 sprays 1X, greater liability for abuse than placebo
- Available by prescription in the UK, EU, Canada, New Zealand & Israel, but not US

**FDA approved Synthetic Cannabinoids (THC)**

- Cesamet (nabilone 1mg capsules) indicated in adults for:
  - Nausea & vomiting associated with cancer who have failed to respond adequately to conventional antiemetic treatments
- Marinol (dronabinol; 2.5, 5, or 10mg doses ) capsules are indicated in adults for:
  - Treatment of anorexia associated with weight loss in patients with AIDS
  - Treatment of nausea and vomiting associated with cancer chemotherapy
  - Patients who have failed to respond adequately to conventional antiemetic treatments
- Syndros (liquid dronabinol) is indicated in adults for:
  - Treatment of anorexia associated with weight loss in patients with AIDS

**Changing Landscape of Marijuana Use**

Cannabis Laws in the U.S.

- States with MMJ vary per:
  - CBD only vs. broad medical use
  - Allowable conditions and routes of administration
  - Dispensaries: home growth and reciprocity
  - Testing, regulatory requirements
### Percentage of Patients Reporting Certain Qualifying Illnesses in Oregon and Colorado

#### Table 1: Number of Reported Drug Substitutions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total Substitutions</th>
<th>PPIs</th>
<th>NSAIDS</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>120</td>
<td>0</td>
<td>0</td>
<td>120</td>
</tr>
<tr>
<td>Back Pain</td>
<td>180</td>
<td>50</td>
<td>0</td>
<td>130</td>
</tr>
<tr>
<td>Arthritis</td>
<td>120</td>
<td>0</td>
<td>0</td>
<td>120</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>80</td>
<td>0</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>Fatigue</td>
<td>60</td>
<td>0</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>Headache</td>
<td>120</td>
<td>50</td>
<td>0</td>
<td>70</td>
</tr>
<tr>
<td>Insomnia</td>
<td>80</td>
<td>0</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>Raynaud’s Syndrome</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Sickle Cell Anemia</td>
<td>60</td>
<td>0</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>Sleeplessness</td>
<td>120</td>
<td>50</td>
<td>0</td>
<td>70</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>40</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

#### References

### Medical Cannabis use in Older Adults Associated with Lower Pain Intensity and Higher Quality of Life

- Older Israeli adult patients (74.5 ± 7.5 yrs) who initiated treatment with medical cannabis
- Common indications were pain (n=1822, 66.6%) and cancer (n=1482, 56.8%), with a significant overlap (i.e., cancer associated pain)
- Cannabis was associated with a reduction in reported pain intensity (median 8 to 4 after 6 months of treatment)
- Before cannabis use, 79.3% of respondents described QoL as “bad” or “very bad”
- 6 mo. Post treatment, 58.6% described QoL as either “good” or “very good”

#### Figure 1: Improvement in Pain with Cannabinoids vs Placebo

- Pain Intensity (0-10)
- Quality of Life

#### Table 2: Terpenes & Pain

<table>
<thead>
<tr>
<th>Terpenes</th>
<th>Effects &amp; Molecular Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limonene</td>
<td>Increased GABA levels</td>
</tr>
<tr>
<td>Myrcene</td>
<td>Reduced hyperalgesia</td>
</tr>
<tr>
<td>α-Terpineol</td>
<td>Reduced nociception</td>
</tr>
<tr>
<td>β-Caryophyllene</td>
<td>Activates cannabinoid receptors</td>
</tr>
<tr>
<td>Pinene</td>
<td>Reduced nociception</td>
</tr>
<tr>
<td>Phytol</td>
<td>Increased GABA levels</td>
</tr>
<tr>
<td>Terpinolene</td>
<td>Increased GABA levels</td>
</tr>
<tr>
<td>Linalool</td>
<td>Increased GABA levels</td>
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</tbody>
</table>

#### References
“Very seldom is the biological activity of the active constituent assayed together with [putative] inactive ‘entourage’ compounds. Investigations of the effect of the active component in the presence of its ‘entourage’ compounds may lead to results that differ from those observed with the active component only.”

Mechoulam R, Ben-Shabat S. Natural Products Reports. 1999;16(2):131-143.

Effect of a Cannabis Sativa Extract in a Rat Model of Neuropathic Pain

- Cannabis sativa, 94.5% CBD, 4% THC with other minor cannabinoids and terpenes reversed thermal hyperalgesia
- These data suggest CBD, THC with other phytochemicals can act synergistically for pharmacologic benefits


2019 NCCIH’s RFA: Exploring the Mechanisms Underlying Analgesic Properties of Minor Cannabinoids and Terpenes

- In 2019 NCCIH made 11 awards to explore the pain-relieving properties and mechanisms of actions of the diverse phytochemicals in cannabis, including both minor cannabinoids and terpenes.
  - Four grants exploring the entourage effect (terpenes + cannabinoids)
  - Three grants exploring the analgesic mechanism of CBD
  - Three grants looking at the analgesic properties of minor cannabinoids
  - One application exploring the analgesic properties of terpenes

Notice of Special Interest (NOSI): Exploring the Mechanisms Underlying Analgesic Properties of Minor Cannabinoids and Terpenes NOT-AT-20-002

- Research emphasis on cannabinoids other than ∆9-THC such as Cannabidiol (CBD), Cannabinol (CBN), Cannabichromene (CBC), and terpenes: Myrrhene, δ-caryophyllene, Limonene, α-terpinene, Linalool, a-phellandrene, α-pinene, η-pinene, α-terpinene, and α-humulene.
- Basic and/or mechanistic studies with model or human volunteers.
- Applicants may use any of the following FOAs: PA-19-055 (R01; clinical trial); PA-19-056 (R01; no clinical trial); PA-19-053 (R21; no clinical trial); PA-19-052 (R21; basic experimental study- humans); PA-19-054 (R21; clinical trial)
- This Notice applies to applications with due dates on or after February 5, 2020 through January 8, 2022

Save the Date: October 24, 2020

Adverse Events
### Individual Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N of Studies</th>
<th>Summary OR 95% CI*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>12</td>
<td>1·98 (0·73, 5·35)</td>
<td>54</td>
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<tr>
<td>Asthenia</td>
<td>14</td>
<td>1·88 (1·26, 2·79)</td>
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</tr>
<tr>
<td>Balance</td>
<td>6</td>
<td>2·62 (1·12, 6·13)</td>
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</tr>
<tr>
<td>Confusion</td>
<td>13</td>
<td>4·03 (2·05, 7·97)</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>15</td>
<td>1·32 (0·87, 2·01)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>17</td>
<td>1·65 (1·04, 2·62)</td>
<td>15</td>
</tr>
<tr>
<td>Disorientation</td>
<td>12</td>
<td>5·41 (2·61, 11·19)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>41</td>
<td>5·09 (4·10, 6·32)</td>
<td>18</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>18</td>
<td>3·68 (2·24, 6·01)</td>
<td>44</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>36</td>
<td>3·50 (2·58, 4·75)</td>
<td>28</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>4</td>
<td>0·83 (0·26, 2·63)</td>
<td>0</td>
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<tr>
<td>Euphoria</td>
<td>28</td>
<td>3·65 (2·00, 6·69)</td>
<td>35</td>
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<tr>
<td>Fatigue</td>
<td>20</td>
<td>2·00 (1·54, 2·62)</td>
<td>0</td>
</tr>
<tr>
<td>Hallucination</td>
<td>10</td>
<td>2·19 (1·02, 4·68)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>2·08 (1·63, 2·65)</td>
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</tr>
<tr>
<td>Paranoia</td>
<td>4</td>
<td>2·05 (0·42, 10·10)</td>
<td>0</td>
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<tr>
<td>Psychosis</td>
<td>2</td>
<td>1·09 (0·07, 16·35)</td>
<td>25</td>
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<tr>
<td>Seizures</td>
<td>2</td>
<td>0·91 (0·05, 15·66)</td>
<td>0</td>
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<tr>
<td>Somnolence</td>
<td>25</td>
<td>2·97 (2·14, 4·12)</td>
<td>24</td>
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<tr>
<td>Vomiting</td>
<td>17</td>
<td>1·67 (1·13, 2·47)</td>
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<tr>
<td>Weakness</td>
<td>1</td>
<td>7·24 (0·36, 145·29)</td>
<td>NA</td>
</tr>
</tbody>
</table>

### DSM-5 Cannabis use Disorders, in the Last 12 Months (2012–2013)

- The CUD prevalence:
  - 12-month: 2.5% (5.98M Americans)
  - Lifetime: 6.27% (14.75M Americans)
- Mean days of marijuana/year:
  - 12-month: 225.3 days
  - Lifetime: 274.2 days
- CUD was associated with other substance disorders, affective, anxiety and personality disorders.
- The odds of cannabis use disorder higher for men, Native Americans, unmarried individuals

### Cannabinoid-Drug Interactions

- **Cannabinoids may inhibit some enzymes**
  - Cannabinoids may induce CYP substrates such as CYP1A2
  - THC & CBD inhibit CYP1A1,1A2 and 1B1 enzymes
  - CBD inhibits CYP2A4, CYP2C19 and others
- **Studies show no effect of oral THC on IV drugs**
- **Medications may augment cannabis effects**
  - Benzodiazepines with cannabis may lead to enhancement of its sedative effects
  - Additive tachcardia may occur with cannabinoids and atropine or amphetamine
- **More research is needed**

### Evidence for Therapeutic Effects Cannabis and Cannabinoids*

- **Conclusive or substantial evidence**
  - For the treatment of chronic pain in adults
  - As anesthetic in the treatment of chemotherapy-induced nausea and vomiting
  - For improving patient-reported multiple sclerosis spasticity symptoms
  - Childhood epilepsy (cannabidiol)
- **Moderate evidence**
  - Improving short-term sleep outcomes with sleep disturbance associated with obstructive sleep apnea syndrome, narcolepsy, chronic pain, and multiple sclerosis
- **Limited evidence**
  - Increasing appetite & decreasing weight loss associated with HIV/AIDS
  - Improving clinician-measured multiple sclerosis spasticity symptoms
  - Improving symptoms of Tourette syndrome (THC capsules)
  - Improving anxiety in individuals with social anxiety disorders (cannabidiol)
  - Improving symptoms of posttraumatic stress disorder (nabilone, a single, small fair-quality trial)
- **No or Insufficient Evidence as an Effective Treatment**
  - Cancers, including glioma
  - Cancer-associated anorexia cachexia syndrome and anorexia nervosa
  - Symptoms of irritable bowel syndrome
  - Spasticity in patients with paralysis due to spinal cord injury
  - Symptoms associated with amyotrophic lateral sclerosis
  - Chorea and certain neuropsychiatric symptoms associated with Huntington’s disease
  - Motor system symptoms associated with Parkinson’s disease
  - Dystonia
  - PTSD
  - Achieving abstinence in the use of addictive substances
  - Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis

Challenges and Barriers in Conducting Cannabis Research

- Despite marijuana being "legal" in some states, the federal government has not legalized cannabis and continues to enforce restrictive policies and regulations
- Cannabis (marijuana) Schedule I
- "Legal" cannabis for research purposes is available only through the NIDA Drug Supply Program
- Products available through the federal system do not sufficiently reflect the variety of products used by consumers
- Investigators must work with FDA (IND), NIDA (LOA), DEA (site licensure), State Boards (controlled substance certificate)

Clinical Practice Challenges

- Health care providers and patients need to know scientific rationale, strength of evidence and implications of medical marijuana laws, and health risks
- Based on current evidence, cannabinoids may have benefit for a limited number of conditions (more data is needed)
- Often lack of knowledge for dosing/frequency of use for effective treatment
- Marijuana has some potential health risks (e.g., addiction, worsening of psychiatric illnesses)
- Lack of FDA and DEA approval presents a real concern for clinical use of MMJ
- Appropriateness of use must be based on risk-benefit analysis
- Variability in product integrity

Current Legislative and Regulatory Landscape

- 2018 Agriculture Improvement Act (Farm Bill)
  - Hemp (< 0.3% THC) is no longer a controlled substance under federal law.
  - Farm Bill preserved FDA’s authority to regulate products containing cannabis or cannabis-derived compounds
  - May 31, 2019- FDA held public hearing to obtain scientific data and information about the safety, manufacturing, product quality, marketing, labeling, and sale of products containing CBD or cannabis-derived compounds
- CBD and THC have been approved as drugs
  - CBD and THC cannot lawfully be added to a food or marketed as a dietary supplement
  - Although FDA can issue regulations to create new exceptions
- Congress is considering several bills to make it easier to conduct research on marijuana products that are available to and used by the public

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