Cannabis and CBD, What is Known for Pain Management?

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Disclosures

- **Employment**
  - University of Texas Health Science Center at San Antonio

- **Consulting**
  - Avanos
  - Medicolegal Expert

- **Fellowship Education Grants**
  - Abbot
  - Boston Scientific

- **Recurring Speaker / Course Director / Leadership / Examiner**
  - American Society of Regional Anesthesia and Pain Medicine
  - American Society of Anesthesiologists
  - American Board of Anesthesiology

- **Investments**
  - Insight Dental Systems
  - iKare MTRC (Behavioral Health)
Objectives

• Review cannabinoids and mechanisms of action.

• Evaluate available evidence for cannabinoids in pain management.

• Evaluate available evidence for adverse effects from cannabinoids.

• Evaluate needs to guide future study and safety surveillance.

The cannabis plant

• Use dates back to over 2000 years B.C.

• Explored as a treatment for compulsive disorders and mental disorders in 1800s

• Described in pharmacopeia as hypnotic, analgesic, and anticonvulsant in early 1900s. This was followed by concerns about use.

• Thereafter made illegal at the state and federal level (Marijuana Tax Act 1937.

• It is specifically still listed under Schedule I by US federal law under the Controlled Substances Act for having "no accepted medical use" and "lack of accepted safety"

<table>
<thead>
<tr>
<th>Chemotype</th>
<th>Δ⁹-THC</th>
<th>CBD</th>
<th>CBD: Δ⁹-THC ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC-type</td>
<td>0.5–15%</td>
<td>0.01–0.16%</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Hybrid</td>
<td>0.5–5%</td>
<td>0.9–7.3%</td>
<td>0.6–4</td>
</tr>
<tr>
<td>CBD-type</td>
<td>0.05–0.7%</td>
<td>1.0–13.6%</td>
<td>&gt;5</td>
</tr>
</tbody>
</table>

NOTE: THCA-predominant strains can yield more than 25 percent Δ⁹-THC; specifically selected CBDA clones can yield up to 20 percent CBD.
Overview - Cannabinoids

• Cannabinoids
  • Diverse (at least 113) family of chemical compounds with diverse effects
  • Act on cannabinoid receptors, a.k.a. endocannabinoid (EC) system
  • Alter neurotransmitter release in the nervous system

• Ligands include
  • natural cannabinoids
  • phytocannabinoids, found in cannabis
  • synthetic cannabinoids

• Phytocannabinoid tetrahydrocannabinol (THC), primary psychoactive compound in cannabis.

Overview – Cannabidiol (CBD) and THC

• Cannabidiol (CBD)
  • Inhibition of endocannabinoid reuptake
  • Transient receptor potential vanilloid 1 receptor activation
  • G protein-coupled receptor 55 activation
  • Augmentation of serotonin 5-HT1A receptors
  • Minimal agonism CB receptors -> negligible psychoactivity
  • Reclassified to Schedule V after FDA approval of Epidiolex
    • (epilepsy from Lennox-Gastaut syndrome and Dravet syndrome)

• THC - (−)-trans-Δ⁹-tetrahydrocannabinol
  • Partial CB1 agonism – principal psychoactive constituent of cannabis
  • CB2 agonism in immune system
  • Positive allosteric modulator of the μ- and δ-opioid receptors
  • Reclassified to Schedule II in 1991 following a recommendation from WHO
  • Possesses mild antioxidant activity sufficient that may protect neurons against oxidative stress
Overview: Dronabinol

• Dronabinol
  • Synthetic delta-9 tetrahydrocannabinol (delta-9-THC)
  • Delta-9-tetrahydrocannabinol is also a naturally occurring component of Cannabis sativa L. (Marijuana).
• Indications
  • Anorexia associated with weight loss in patients with HIV/AIDS
  • Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.
• Formulations
  • 2.5, 5.0, 10 mg capsules

Overview - Nabiximols

• Nabiximols
  • Cannabis Extract with principal active cannabinoid components
    • THC
    • CBD
• Approved as a botanical drug in United Kingdom
  • Uses include spasticity, overactive bladder, neuropathic pain, MS symptoms
• Trade formulation spray delivers a dose of 2.7 mg THC and 2.5 mg CBD.
Overview: Levonantradol and Ajulemic acid

• Levonantradol
  • synthetic cannabinoid analog of delta(9)-THC
  • 30x more potent than THC
  • antiemetic and analgesic effects
  • CB1 and CB2 agonist.

• Clinically tested in cancer patients esp. for chemo induced nausea

• Originally studied as an IM formulation given every 4 hours (0.5-4mg)

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Overview: Nabilone

• Nabilone
  • Synthetic analog of delta-9-tetrahydrocannabinol (Δ⁹-THC)
  • Weak partial agonist CB1 and CB2
  • 2x as active as Δ⁹-THC

• Indication
  • FDA approved for nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments

• Ajulemic acid
  • Synthetic cannabinoid derivative of the THC metabolite 11-nor-9-carboxy-THC
  • Anti-fibrotic and anti-inflammatory effects in pre-clinical studies
  • Lacks substantial psychoactive effects
  • CB2 agonist -> lipoxin A4 and Prostaglandin J2

• Potential applications: systemic sclerosis, dermatomyositis and cystic fibrosis
Hemp Seed, CBD, Cannabis oils

### TABLE 1. Hemp Seed, CBD, and Cannabis Oils

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hemp seed oil $^{10}$</th>
<th>Hemp/CBD oils $^{12}$</th>
<th>Cannabis oils $^{22,41}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part of plant taken</td>
<td>Seeds</td>
<td>Flowers and leaves of hemp plant</td>
<td>Flowers and leaves of marijuana plant</td>
</tr>
<tr>
<td>Main components</td>
<td>Omega-6 and omega-3 fatty acids, γ-linolenic acid, nutritious antioxidants</td>
<td>Mostly CBD and BCP with other smaller-quantity phytocannabinoids and terpenoids</td>
<td>Mostly THC with some CBD and other phytocannabinoids and terpenoids</td>
</tr>
<tr>
<td>THC levels</td>
<td>None</td>
<td>&lt;0.3% Dry weight</td>
<td>&gt;0.3% Dry weight (often very high amounts such as 80%)</td>
</tr>
<tr>
<td>CBD levels</td>
<td>Little to none</td>
<td>More than average cannabis plants (12%-18% CBD, often higher due to postextraction enrichment)</td>
<td>Lower levels (10%-15%)</td>
</tr>
<tr>
<td>Uses</td>
<td>Nutritional supplement, other uses of hemp such as clothing and fibers</td>
<td>Medicinal uses of CBD and full-spectrum hemp oils</td>
<td>Medicinal uses of THC</td>
</tr>
</tbody>
</table>

BCP = β-caryophyllene; CBD = cannabidiol; THC = tetrahydrocannabinol.


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**PAIN**

The endocannabinoid system and neuropathic pain

- G protein-coupled cannabinoid receptors CB1 & CB2
- CB1
  - Primarily central CNS
- CB2
  - Immune modulation
  - Inhibition of neuropathic processes

The Cannabinoid CB2 Receptor as a Target for Inflammation-Dependent Neurodegeneration

John C. Abbott$^1$ and Michelle Glass$^2$

$^1$Department of Pharmacology & Toxicology, University of Otago, New Zealand; $^2$Department of Pharmacology, University of Auckland, New Zealand
Endocannabinoid (EC) System

Theoretical Pain Strategies involving the EC

• FAAH Inhibition for Analgesia (degradative enzyme)
• MAGL Inhibition for Analgesia (degradative enzyme)
• Positive Allosteric modulators of cannabinoid CB1 receptor signaling
  • “Because allosteric modulators bind to sites distinct from the orthosteric binding site, they might be expected to show a more limited spectrum of unwanted cannabimimetic effects compared to direct agonists like THC.”

• Stress-Induced Modulation of Pain
  • Stress-Induced Analgesia and Hyperalgesia (SIH)
• The EC System & Medial Prefrontal Cortex (mPFC) Dysfunction / mGluR5
EC receptors

- CBD 1R
- CBD 2R – mostly peripheral organs and immune system
- Receptor interaction:
  - THC (tetrahydrocannabinol) – CB1/2 partial agonist
  - CBN (cannabinol) – partial agonist CB2>CB1, less potent
- Allosteric interaction
  - CBD (cannabidiol) antagonist of CB1/CB2 receptor agonists in CB1- and CB2-expressing cells or tissues

The diverse CB₁ and CB₂ receptor pharmacology of three plant cannabinoids: Δ⁹-tetrahydrocannabinol, cannabidiol and Δ⁹-tetrahydrocannabivarin

RG Pertwee
School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK

That CBD can behave as a CB₂ receptor inverse agonist may account, at least in part, for its well-documented anti-inflammatory properties (Pertwee, 2004b) as there is evidence that CB₂ inverse agonism can inhibit immune cell migration and reduce clinical signs of inflammation (Lunn et al., 2006) and that CBD is a potent inhibitor of evoked migration in the Boyden chamber both of murine microglial cells and macrophages (Walter et al., 2003; Sacerdote et al., 2005) and of human neutrophils (McHugh and Ross, 2005).

**Therapeutic Areas**
- Chronic pain
- Cancer – chemotx induced N/V
- Anorexia
- IBS
- Epilepsy
- Spasticity d/t MS or SCI
- Tourette Syndrome
- Amyotrophic lateral sclerosis
- Huntington’s disease
- Parkinson’s disease
- Dystonia
- Dementia
- Glaucoma
- Traumatic Brain Injury
- Addiction
- Anxiety
- Depression
- Sleep disorders
- PTSD
- Schizophrenia & psychoses

**Studied Compounds**
- Dronabinol
- Nabiximols
- Levonantradol
- THC

**Studied Conditions**
- N/V due to chemo
- Appetite Stimulation (AIDS)
- Chronic Pain
• Chronic Pain Trials
  • Nabiximols
  • Smoked THC
  • Nabilone
  • Vaporized cannabis
  • Ajuvenic acid
  • Oral THC

• Conditions studied
  • Peripheral/Central neuropathic pain
  • Diabetic peripheral neuropathy
  • HIV neuropathy
  • Pain due to MS
  • Chemotherapy induced
  • Central pain
  • Cancer pain
  • Fibromyalgia
  • Rheumatoid Arthritis
  • Non-cancer (nociceptive/neuropathic)
  • Musculoskeletal pain

Outcomes
• 17/28 trials with high risk of bias
• MCID: 30% reduction in pain v. placebo
• Performance (no. trials):
  • (8) Cannabinoids: OR 1.41 [95% CI, 0.99-2.00]
  • (1) Smoked THC: OR 3.43 [95% CI, 1.03-11.48] +
  • (7) Nabiximols ++ : outperformed placebo on
    • Numerical Rating Scale 0-10 (WMD -0.46)
    • Brief pain inventory-short form, severity composite index
    • Neuropathic pain scale,
    • Proportion improved on global impression of change
  • (6) Neuropathic Pain: OR 1.38 [95% CI, 0.93-2.03]
  • (2) Cancer pain: OR 1.41 [95% CI, 0.99-2.00]
Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies

Emily Stockings1*, Gabrielle Campbell2, Wayne D. Holford3, Suzanne Nielsen4, Dino Zager5, Ramin Rahman6, Brijh Matharu7, Michael Pappin8, Megan Wells9, Lucid Degenhardt10

- 104 studies on CNCP following IMMPACT guidelines
- 47 RCT, 57 Observational
  - (48) Neuropathic Pain
  - (7) Fibromyalgia
  - (1) Rheumatoid Arthritis
  - (13) MS related pain
  - (6) Visceral pain
  - (29) Mixed or undefined

“There were no significant impacts on physical or emotional functioning, and low-quality evidence of improved sleep and patient global impression of change”

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

Penny F. Witting, PhD; Robert F. Wolff, MD; Susan Deshpande, MSc; Marcello De Nisi, PhD; Steven Duffy, PhD; Adriana V. Hernandez, MD, PhD; J. Christiana Neumann, MD, PhD; Shawn Lang, PhD; Kate Mace, MSc; Steve Ryder, MSc; Simone Schmoller, MSc; Marie Wenigau, PhD; Jia Kleiner, MD, PhD

<table>
<thead>
<tr>
<th>Improvement in Pain With Cannabinoid vs Placebo by Study</th>
<th>Cannabinoid Events</th>
<th>Placebo Events</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrahydrocannabinol (smoked)</td>
<td>No.</td>
<td>Total No.</td>
<td>No.</td>
</tr>
<tr>
<td>Abrams et al,77 2007</td>
<td>13</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>Nabiximols</td>
<td>No.</td>
<td>Total No.</td>
<td>No.</td>
</tr>
<tr>
<td>GW Pharmaceuticals,22 2005</td>
<td>54</td>
<td>149</td>
<td>59</td>
</tr>
<tr>
<td>Johnson et al,69 2010</td>
<td>23</td>
<td>53</td>
<td>12</td>
</tr>
<tr>
<td>Langford et al,65 2013</td>
<td>84</td>
<td>167</td>
<td>77</td>
</tr>
<tr>
<td>Nurmikko et al,76 2007</td>
<td>16</td>
<td>63</td>
<td>9</td>
</tr>
<tr>
<td>Portenoy et al,67 2012</td>
<td>22</td>
<td>90</td>
<td>24</td>
</tr>
<tr>
<td>Selvarajah et al,70 2010</td>
<td>8</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Serpell et al,88 2014</td>
<td>34</td>
<td>123</td>
<td>19</td>
</tr>
<tr>
<td>Subtotal ( I^2 = 44.5% ) ( P = 0.94 )</td>
<td>241</td>
<td>660</td>
<td>209</td>
</tr>
<tr>
<td>Overall ( I^2 = 47.6% ) ( P = 0.64 )</td>
<td>254</td>
<td>685</td>
<td>215</td>
</tr>
</tbody>
</table>

• Duration of treatment/active follow-up

<table>
<thead>
<tr>
<th>Number</th>
<th>Unit</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Days</td>
<td>HIV neuropathic</td>
</tr>
<tr>
<td>14</td>
<td>Weeks</td>
<td>Painful Diabetic Neuropathy</td>
</tr>
<tr>
<td>14</td>
<td>Days</td>
<td>Cancer pain</td>
</tr>
<tr>
<td>14</td>
<td>Weeks</td>
<td>MS central pain</td>
</tr>
<tr>
<td>5</td>
<td>Weeks</td>
<td>Allodynic Neuropathic pain</td>
</tr>
<tr>
<td>7</td>
<td>Weeks</td>
<td>Cancer pain (opioids)</td>
</tr>
<tr>
<td>12</td>
<td>Weeks</td>
<td>Painful Diabetic Neuropathy</td>
</tr>
<tr>
<td>14</td>
<td>Weeks</td>
<td>Allodynic Neuropathic pain</td>
</tr>
</tbody>
</table>

No study had longer than 14 weeks of treatment

• Outcomes
  - 30% pain reduction
    - 29% cannabinoids
    - 25.9% placebo
    - NNT = 24
  - 50% pain reduction – no diff.
    - 18.2% cannabinoids
    - 14.4% placebo
  - Pooled mean difference 3mm on 100 mm VAS v placebo

• Adverse events
  - 81.2% cannabinoids
  - 66.2% placebo
  - NNH = 6
Short term efficacy and tolerability

- THC dosing (aerosol)
  - Placebo
  - Low 1% THC
  - Medium 4% THC
  - High 7% THC
- Patient observed over 3 hours
- Spontaneous, evoked pain and neuropsychological testing

Outcomes

- Spontaneous pain reduced in dose dependent fashion.
- Evoked pain reduced in high dose grp.
- Reduced performance in high dose grp. on Paced Auditory Serial Addition Test, Trail Making Test Part B

<table>
<thead>
<tr>
<th>Formulations (Cannabis vapor)</th>
<th>Double blind, placebo controlled, 4-way crossover - Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) 22% THC; 1% CBD</td>
<td>Increased pressure tolerance with A, B</td>
</tr>
<tr>
<td>B) 6.5% THC; 8% CBD</td>
<td>B improved spontaneous pain (below)</td>
</tr>
<tr>
<td>C) &lt;1% THC; 9% CBD</td>
<td></td>
</tr>
<tr>
<td>D) placebo derived from Bedrocan cannabis</td>
<td></td>
</tr>
</tbody>
</table>

- Excluded: patients on strong opioids, benzos
- 180 minutes observation

• “This is a pivotal time in the world of cannabis policy and research. Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives.”

• Recommendations:
  • Address Research Gaps
  • Improve Research Quality
  • Improve Surveillance Capacity
  • Address Research Barriers

• Conclusions – Substantial Evidence for an effect in
  • Treatment of chronic (neuropathic) pain
  • Chemotherapy induced nausea
  • MS spasticity symptoms

• Recommendations:
  • Address Research Gaps
  • Improve Research Quality
  • Improve Surveillance Capacity
  • Address Research Barriers

- Substantial evidence for associations with adverse health conditions:
  - Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term use)
  - Increased motor vehicle crashes
  - Lower birth weight of the offspring
  - The development of schizophrenia or other psychoses, with the highest risk among the most frequent users

- Moderate evidence:
  - Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal
  - The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use)
  - Increased symptoms of mania and hypomania (in bipolar individuals)
  - Small increased risk for the development of depression
  - Increased incidence of suicidal ideation and suicide attempts
  - Increased incidence of social anxiety disorder

Development of Problem Cannabis Use – Risk Factors

- Substantial evidence:
  - Male + smoking cigarettes
  - Initiating cannabis at earlier age
  - Increased frequency -> progression
  - Male -> increased severity

- Moderate evidence:
  - Major depressive disorder
  - Exposure to the combined use of abused drugs
  - During adolescence
    - frequency of cannabis use
    - oppositional behaviors,
    - younger age of first alcohol use
    - nicotine use,
    - parental substance use,
    - poor school performance,
    - antisocial behaviors,
    - childhood sexual abuse
There is moderate evidence of a statistical association between cannabis use and:

The development of substance dependence and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs

Address Research Gaps

- National funding and support
- At-risk or under-researched populations, youth
- Pharmacodynamics, Dose response
- Study lesser known cannabis products
- Study health effects of different routes of administration (e.g. inhaled)
- Investigate economic impact of recreational and medical cannabis
- Evaluate quality assurance, safety, labelling/packaging standards
Improve Research Quality

• Should involve HHS, CDC, and other agencies
• Develop conclusive evidence on short and long-term effects (benefits and harms)
• Minimum standards for study design, sufficient datasets
• Guidelines for data collection methods
• Development of uniform terminology
• Development of databanks for clinical research and public health surveillance

Improve Surveillance Capacity

• State and federal public surveillance efforts should be supported by state and local public health departments, the CDC, SAMHSA, Association of State and Territorial Health Officials, National Association of County and City Health Officials, the Association of Public Health Laboratories
• Develop question banks for incorporation into major public health surveys
• Determine capacity to collect and codify data (e.g. ICD-10)
• Establish state testing facilities to analyze composition of products
• Diagnostic technologies to assess cannabis exposure and impairment
• Strategies to surveil adverse effects of therapeutically used cannabis
Address Research Barriers

• CDC, NIH, USDA, industry groups, nongovernmental organizations should convene experts to characterize impacts of regulatory barriers to research and assess needs to conduct a comprehensive cannabis research strategy
• Propose strategies for expanding access to research-grade marijuana
• Investigating strategies for improving the quality, diversity, and external validity of research-grade cannabis products
• Identifying non-traditional funding sources for research


FDA

• “FDA continues to be concerned at the proliferation of products asserting to contain CBD that are marketed for therapeutic or medical uses although they have not been approved by FDA. Often such products are sold online and are therefore available throughout the country. Selling unapproved products with unsubstantiated therapeutic claims is not only a violation of the law, but also can put patients at risk, as these products have not been proven to be safe or effective. This deceptive marketing of unproven treatments also raises significant public health concerns, because patients and other consumers may be influenced not to use approved therapies to treat serious and even fatal diseases.”

Summary

- Cannabinoids appear to have analgesic effects for neuropathic pain; treatment effects may be modest.
- Results for Chronic Non-cancer Pain (CNCP) are weak, with NNT>>NNH.
- Most studies were performed on drugs not available in the United States – i.e. Nabiximols (Sativex)
- CBD is theorized to be useful for pain but may have an antagonistic effect with THC and remains poorly studied or regulated
- Smoked THC and other forms of THC may increase risk of motor vehicle collisions, low birth weight, respiratory diseases, addiction, psychosis, and mood disturbances or mood disorders; it may also lead to Problematic Cannabis Use disorder.
- Significant research barriers must be reconciled in the USA for better quality long-term data on benefits/harms.