Medical Marijuana, Pain, and the Pharmacology of Cannabinoids

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Presentation Outline

1) Pharmacology of the cannabinoids

2) Recent trends in marijuana use

3) Approved uses, and rationale for the use of medical marijuana for pain

4) Potential for drug-induced short and long term adverse events
The Oregon Medical Marijuana Act

• **1998** Oregon voters approved Ballot Measure 67
• Allowed the use of marijuana for debilitating medical conditions
• Established a state-controlled permit system to administer and oversee the Act (Oregon Heath Authority)
  – the Oregon Medical Marijuana Program (OMMP)
• Act is intended to allow Oregonians (with debilitating conditions) to discuss the use of marijuana and protect patients and doctors from penalties
• **January 2014** the Oregon State Legislature approved the establishment of *Medical Marijuana Dispensaries* *(OHA)* (307 Dispensaries and 121 Processing Sites)

• **July 2015** recreational marijuana became legal for personal use

• **October 2015** early sales of recreational marijuana allowed at medical dispensaries (until Dec 31, 2016)

• **October 2016** recreational marijuana stores open *(OLCC)*

• **January 2017** all retail sales must now be from an establishment that is registered with OLCC
Cannabis sativa, American Medicinal Plants, 1887

Charles F. Millsbaugh, National Library of Medicine
Other Medicinal Plants, texts from 1817-1839

Nicotiana tabacum

Vitus vinifera

Erythroxylon coca

Papaver somniferum

National Library of Medicine
Circa 1885

Cocaine was the first natural product local anesthetic

Adapted from *Cocaine and Dentistry* (2013) N.Calceterra
Medicinal use of American Cannabis

1854  Listed in U.S. Dispensatory Tincture of Cannabis made by many companies e.g. Parke-Davis, Eli Lilly, Bristol-Meyers Squibb, Merck

Used for:
• Insomnia
• Headaches
• Sexual dysfunction
• Eating disorders

1937  Marijuana Tax Act
1941  Removed from American Pharmacopoeia
What is Medical Marijuana?

- A general term
- Cannabinoids are found:
  1. **Endogenously** – endocannabinoid system
  2. **Plant natural products** – numerous phytochemicals in the *Cannabis* plant (e.g. Δ9-THC and cannabidiol)
  3. **Synthetic forms** – pharmaceutical grade Δ9-THC and a close isomer
Natural cannabinoids are secondary metabolites that help the plant adapt to its environment.
Plant-derived Cannabinoids

400 + compounds
66 – 90 “Cannabinoids”

1930s Cannabinol (CBN) and Cannabidiol (CBD) isolated
1942 Δ⁹- tetrahydrocannabinol (THC) isolated
1964 (±)-Δ⁹THC and then (±)-CBD synthesized
1970 Marijuana listed as a Schedule I substance (negatively impacting research)
1990 CB₁ cannabinoid receptor cloned
1993 CB₂ cannabinoid receptor cloned
... development of **single molecule oral** drugs
Two have been approved by the U.S. Food and Drug Administration (FDA) via the normal process:

**Dronabinol (Marinol®) 1992**
\(\Delta^9\)-THC
For severe nausea & loss of appetite resulting in weight loss (**schedule III**)

**Nabilone (Cesamet®) 1985**
Synthetic analogue
For severe nausea (**schedule II**)
Adjunct for neuropathic pain
Life of an U.S. FDA approved medicine

- **Phase IV**: Post market surveillance

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**Stages of Clinical Trials**

- **Lab Studies**: Several Years
- **Human Safety**: Days or Weeks
- **Expanded Safety**: Weeks or Months
- **Efficacy & Safety**: Several Years

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- **Cesamet**
- **Marinol**: Capsules

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**Image**: Medication and marijuana plant.
Δ⁹-tetrahydrocannabinol (THC) is the main psychoactive substance in *Cannabis sativa*

*Cannabis indica* plant is particularly high in THC – now many hybrid strains

THC binds to both Cannabinoid Receptors (CB₁ and CB₂) with relatively good affinity \((Ki = 5-80 \text{ nM})\)
CB₁ is considered the most abundant GPCR in the brain

Orphan receptors
(activated by “exogenous” cannabinoids)

GRP55
Cannabinoid receptor localization in brain
(tetrahydrocannabinol/autoradiography/basal ganglia/hippocampus/cerebellum)

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[3H]CP 55,940 Autoradiography

PET imaging (NIMH)
Endogenous Cannabinoids are Neuromodulators

- **CB₁** receptors are primarily located on **presynaptic neurons** to inhibit neurotransmitter release
- **CB₂** receptors are primarily located on immune cells, periphery and on **microglia**
- Endogenous agonists for these receptors are lipid mediators - the **endocannabinoids** (isolated 1992 - 1995) – these ligands may also act at other targets
Synaptic Neuromodulation

**Plant-derived cannabinoid**

- THC

**Endogenous cannabinoids**

- AEA
- 2-AG

**Presynaptic neuron**

- CB1 receptor
- Neurotransmitters
- ↓Ca²⁺

**Postsynaptic neuron**

- Precursor
- ↑Activity (for example, ↑Ca²⁺ concentration)

Nature Reviews | Cancer
The acute action of Δ⁹-THC is to cause PRESYNAPTIC INHIBITION.
Endogenous agonists are arachadonic acid derivatives

Anandamide (AEA), 2-arachidonoylglycerol (2-AG)

Bioactive lipids synthesized from membrane precursors

Production is activity-dependent

Terminated by hydrolysis (Enzymes are potentially future drug targets)
Crystal Structure of the Human Cannabinoid Receptor CB₁

Tian Hua,¹,² Kiran Vemuri,³ Mengchen Pu,² Lu Qu,¹,² Gye Won Han,⁴ Yiran Wu,¹ Suwen Zhao,¹ Wenqing Shui,¹ Shanshan Li,¹ Anisha Korde,³ Robert B. Laprairie,⁵ Edward L. Stahl,⁵ Jo-Hao Ho,⁵ Nikolai Zvonok,³ Han Zhou,³ Irina Kufareva,⁶ Beili Wu,⁷ Qiang Zhao,⁷ Michael A. Hanson,⁸ Laura M. Bohn,⁵,* Alexandros Makriyannis,³,* Raymond C. Stevens,¹,⁴,⁹,* and Zhi-Jie Liu¹,²,*

- Ligand-bound structure stabilized by antagonist
- Ligand docking allows prediction of interactions with THC and synthetic cannabinoids
How do people use marijuana?

**Smoke** (hand-rolled joints; pipes; water pipes)

**Vaporize** (inhaled vapor)

**Ingest** (“edibles”; “teas”)

**Topically** (oils; creams – mainly marketed for local action)

Dried: flowers, leaves, stems, seeds
Profiling marijuana (what dose?)

- Most dispensaries sell multiple strains of medical marijuana
- Quality control is based on analytical testing of plant material to yield a cannabinoid potency profile
  % weight cannabinoids/total plant weight

Examples:

- % THC-total - $\Delta^9$-THC, $\Delta^8$-THC, CBN
  $$< 9\% = \text{LOW THC and} \quad >> 14\% = \text{HIGH THC}$$

- % CBD-total – Cannabidiol
  $$< 1\% = \text{LOW CBD and} \quad > 4\% = \text{HIGH CBD}$$

Dose for edibles is listed in mg
(e.g. 5 mg THC = 1 serving)
Steady Increase in Potency – start low go slow!

Figure 1. Increases over Time in the Potency of Tetrahydrocannabinol (THC) in Marijuana and the Number of Emergency Department Visits Involving Marijuana, Cocaine, or Heroin.

NEJM
370: 2219
2014
Medicinal patients have access to higher maximum concentrations/serving size

<table>
<thead>
<tr>
<th>Type of Marijuana Item</th>
<th>Maximum Concentration or Amount of THC Per Serving</th>
<th>Maximum Concentration or Amount of THC in Container</th>
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<tbody>
<tr>
<td>Cannabinoid Edibles</td>
<td>N/A</td>
<td>100 mg</td>
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<tr>
<td>Cannabinoid Topicals</td>
<td>N/A</td>
<td>6 %</td>
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<td>Cannabinoid Tinctures</td>
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<td>Cannabinoid Capsules</td>
<td>100 mg</td>
<td>4,000 mg</td>
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<tr>
<td>Cannabinoid Suppositories</td>
<td>100 mg</td>
<td>4,000 mg</td>
</tr>
<tr>
<td>Cannabinoid Transdermal Patches</td>
<td>100 mg</td>
<td>4,000 mg</td>
</tr>
<tr>
<td>Cannabinoid Concentrates or Extracts</td>
<td>N/A</td>
<td>4,000 mg</td>
</tr>
<tr>
<td>Cannabinoid Products Other than Cannabinoid Edibles, Topicals, Tinctures, Capsules, Suppositories or Transdermal Patches</td>
<td>N/A</td>
<td>4,000 mg</td>
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</table>
Hashish/hash – traditionally made from trichomes / resin glands from female plants

**Cannabis concentrates**

**Dabbing** - flash vaporization of cannabis concentrate with a solvent (e.g. butane) - hot surface (nail) – inhaled (water pipe)
Higher potency (80% ?)
Butane Hash Oil, shatter, wax, honeycomb, crumble

**Dangers**!
Heat – blow torch
Contaminants
High potency THC
Separating Recreational and Medicinal Use of Marijuana

(1) Different primary motivation/goal

**Symptom relief** versus **pleasure**

(2) Preferred route of administration may / may not differ

**Smoking** – rapid and predictable bioavailability (allows self titration)

**Vapor** – release of cannabinoids without smoke combustion products

**Oral** – poorer bioavailability “edibles” have a longer activation time
Qualifying Medical Conditions

• Cancer
• Glaucoma
• Degenerative/pervasive neurological conditions
• HIV/AIDS
• Post Traumatic Stress Disorder (PTSD)
• A medical condition with:
  – Severe Pain
  – Severe Nausea
  – Seizures (including but not limited to epilepsy)
  – Persistent muscle spasms (including but not limited to those caused by Multiple Sclerosis)
<table>
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<tr>
<th>Category</th>
<th>Count</th>
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<td>Patients</td>
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<tr>
<td>Caregivers</td>
<td>28,368</td>
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<tr>
<td>Growers</td>
<td>36,354</td>
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<td>Grow Sites</td>
<td>26,631</td>
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<tr>
<td>Physicians</td>
<td>1,722</td>
</tr>
</tbody>
</table>

- Physicians: 1,722 with 1 to 449 patients
- 24 with 450+ patients
Patients by Condition (Jan 2017)

- Severe Pain: 60,683
- Spasms: 19,170
- Nausea: 8,713
- PTSD: 5,501
- Cancer: 4,284
- Seizures: 1,819
- Glaucoma: 967
- Cachexia: 953
- Neurological: 912
- HIV/AIDS: 579
Marijuana for management of persistent chronic pain, neuropathic pain, cancer pain & muscle spasms

- **Endogenous cannabinoids** modulate pain perception under physiological conditions

- Good evidence that synthetic and endogenous cannabinoids are analgesic

- Activation of cannabinoid receptors **induces analgesia** in many animal models
Cross-talk between two endogenous systems to modulate pain perception

Endogenous opioid peptides (Met-enkephalin and Leu-enkephalin)
Opioid (mu, delta) Receptors

Endogenous cannabinoids (lipid modulators)
Cannabinoid (CB$_1$) Receptors
Cannabinoid receptors are located in the brain, spinal cord and periphery.

Co-expressed with opioid receptors in the dorsal horn of the spinal cord.

Inhibit pro-nociceptive peptides and glutamate-dependent excitation.
Cannabinoids hypothesized to act on Descending Pathways for Pain Perception

Periaqueductal grey (PAG)
rostral ventromedial medulla (RVM)
dorsal horn (DH)

GABA “dis-inhibition” of this axis
January 2017 – extensive review of available evidence (randomized controlled trials)

Conclusive or Substantial Evidence
• cannabis is effective for treatment of chronic pain in adults
• oral cannabinoids are an effective treatment for improving patient-reported M.S. spasticity symptoms

Limited Evidence
....for an effect on clinician-measured spasticity
Cannabidiol (CBD)

- Does not bind CB$_1$ or CB$_2$
- Considered non-psychoactive
- Emerging hypothesis that CBD binds FABP to inhibit degradation of endogenous cannabinoid ligands
- 2013 Orphan Drug Designation granted for a purified extract of (99% CBD (Epidiolex®) to treat children with two different intractable epilepsy syndromes (randomized trials)

Deutsch (2016)
Frontiers in Pharmacology 7: 370
Efficacy of combined THC + CBD

- **Sativex®** is a standardized pharmaceutical product containing THC:CBD (2.7 mg/2.5 mg)
- Approved in Canada, Australia, UK, Spain + others for Persistent muscle pain of Multiple Sclerosis
- If approved - expense may not prove to be “cost-effective” relative to medical marijuana

**Sativex®** is currently in several active phase III clinical trials in the US for cancer pain – *FDA fast track*
- persistent pain in advanced cancer
- uncontrolled pain/unmet need
Nabiximols (Sativex ®; GW Pharmaceuticals)

- Non-opioid analgesic
- Endocannabinoid system modulator
- Suggests a role for endocannabinoids in spasticity – clear mechanism to account for efficacy is lacking
Marijuana as medicine... general considerations

(1) Psychoactive effects may not be tolerated especially in naïve users that have no prior experience

(2) Definitive evidence for most therapeutic effects is still limited

(3) Issues associated with a non-pharmaceutical grade product (quality control, batch variation, dosing, patient counselling at “point of sale” from individuals that may lack medical training)
Early onset side-effects

(1) Increased heart rate

(2) Vasodilation

(3) Decreased heart rate and lower blood pressure

(4) Red eyes (dilation of capillaries in the eyes); pupils may dilate, blurred vision
Potential Adverse Effects

(1) Impaired short-term memory – may compromise ability to learn and retain information

(2) Impaired motor co-ordination – e.g. driving skills

(3) Altered judgment and perceptions of safety

These are all predicted by actions of marijuana as a neuromodulator of CNS signaling and largely considered reversible upon abstinence
Recognized Adverse Effects

(1) Frequency of use increases the likelihood of developing problematic use (cannabis and other substances)

(2) Negative effect on pre-existing psychiatric illness risk
   • worsening symptoms; medical marijuana is not advised in these patients

(3) Symptoms of bronchitis in habitual smokers
   • Increase in cough, sputum production, wheezing
   • Symptoms are similar to cigarette smokers and additive
Cannabinoid Hyperemesis Syndrome

• Counterintuitive (first described in 2004)
• Associated with chronic, heavy use of cannabis (presumably recreational or medical)
• Recurrent episodes of severe nausea, retching and cyclical vomiting in the absence of other pathology
• Abdominal pain, temporary relief from hot showers/baths triggering compulsive showering!
• Symptoms stop after cannabinoid cessation but resume within weeks of resuming
Metabolism and Elimination

1. Substrate of Cytochrome P450 CYP3A4 and CYP2C9

2. Cannabinoids are lipophilic – relatively long elimination

3. Renal elimination (50 ng/mL cutoff urine test)
   THC is metabolized to a metabolite, 1-nor-9-carboxy-Δ9-tetrahydrocannabinol (THCCOOH), conjugated with glucuronic acid and eliminated in urine

Very long "detection times" in habitual users 27 days versus 3 days – complicates interpretation of "new" versus "past" use in the workplace by immunoassay
Drug – Drug interactions

(1) CNS actions of marijuana: impaired cognitive function and motor function caution against combining medical marijuana with sedatives/hypnotics (benzodiazepenes, medications for insomnia, barbiturates, anti-histamines) and other central acting medications including alcohol

(2) Multiple anecdotal reports of interactions– intensifies side effects or changes marijuana response/experience

(3) We are in a phase of post-market evaluation – so far relatively safe in monotherapy!
Summary

(1) There are large gaps in our knowledge of the endocannabinoid system - but the potential for potentiation of analgesia allowing a reduction in the dose of opioids should be pursued

(2) Medical marijuana users have a significant burden of chronic disease and unmet need for alternatives

(3) THC is the best studied natural cannabinoid but the mechanistic basis of medical marijuana (i.e. the mixture of compounds) is not understood
In global first, Teva signs deal to market medical marijuana inhaler

Tel Aviv-based Syqe Medical says its device revolutionizes precise delivery of the drug, already in use in Haifa hospital

BY SHOSHANNA SOLOMON | November 28, 2016, 12:00 pm | 

- Delivers a metered/selective dose of vaporized “botanical”
- Pharmaceutical grade cannabis capsules
Thank you for inviting me!