Medical Cannabis and Pain
Collaborators

Milken Institute School of Public Health
THE GEORGE WASHINGTON UNIVERSITY

GEORGETOWN UNIVERSITY
More resources available at the DC Center for Rational Prescribing

doh.dc.gov/dcrx
Course Faculty

• Donald I. Abrams, MD
• Adriane Fugh-Berman, MD
• Mikhail Kogan, MD
• Susan Wood, PhD
Important Information

- The video will progress at its own pace.
- Do not attempt to speed up the video.
- The post-test will only unlock after viewing the entire video.
- The video can be paused and resumed later.
Course Objectives

After completing this module, participants should be able to...

- Differentiate characteristics of cannabinoid receptors.
- List three appropriate uses for medical cannabis.
- Compare advantages and disadvantages of different routes of cannabis administration.
- Describe the relationship between opioids and cannabinoids.
Cannabis and Pain

Donald I. Abrams, MD
Chief, Hematology-Oncology
Zuckerberg Francisco General Hospital
Professor of Clinical Medicine, UCSF
Conflicts of Interest

Dr. Donald Abrams discloses that he has financial relationships with the following companies.

- ABcann
- AXIM Biotechnologies, Inc
- Maui Wellness Group
- Scriptyx
- Tikun Olam
Cannabis May Have Eased Breast Cancer Symptoms of Siberian Ice Princess

October 17, 2014 | by Lisa Winter

photo credit: Kobsev via Wikimedia Commons
Cannabis as Medicine

- Marijuana (cannabis, hemp) is one of the oldest known psychoactive plants
- First reported use as medicine ~3,000 years ago
- Introduced into Western medicine in 1840s by Dr. W.B. O’Shaughnessy
- Promoted for putative analgesic, sedative, anti-inflammatory, antispasmodic and anticonvulsant properties
Additional products available in 1906 manufactured by Eli Lilly, Wyeth, Sharp & Dohme
Cannabis as Medicine

• Interest waned in early 1900s with advent of opiates, barbiturates, chloral hydrate, aspirin and syringes

• First federal restrictions in 1937 with Marihuana Tax Act ($1/oz for medical use, $100/oz for recreational users)

• AMA was virtually alone in opposing act.
  • Believed objective data re: harmful effects were lacking
  • Act would impede future clinical investigations

• Removed from US Pharmacopoeia in 1942
The Health Effects of Cannabis and Cannabinoids:
The Current State of Evidence and Recommendations for Research
Cannabinoid Receptors

- CB₁ and CB₂ receptors identified
- Receptors encoded by separate genes on separate chromosomes; share 48% amino acid identity
- G-protein coupled receptors that inhibit adenylyl cyclase on activation
  - Decreases cyclic AMP and protein kinase A activity
  - Inhibition of Ca²⁺ influx through various Ca²⁺ channels
  - Stimulation of inwardly rectifying K⁺ channels and mitogen-activated protein kinase cascades
Cannabinoid$_1$ Receptor

- CB$_1$ receptors identified throughout central and peripheral nervous system
  - Density highest in cingulate gyrus, frontal cortex, hippocampus, cerebellum and basal ganglia
- CB$_1$ receptors present in virtually all organs and tissues of the body
Cannabinoid\textsubscript{2} Receptor

- CB\textsubscript{2} receptor originally detected in macrophages and marginal zone of the spleen
- Largest concentration in peripheral blood present in B-cells and NK cells
- Also found in bone and to a lesser degree in liver and nerve cells
Endocannabinoids

Anandamide

Di-homo-\(\gamma\)-linolenoylethanolamide

Docosatetraenoylethanolamide

2-Arachidonoyl-Glycerol

CB1
Suppression of Neurotransmitter Release

- Serotonin (5-HT)
- Glutamate
- Acetylcholine
- GABA
- Noradrenaline
- Dopamine
- D-aspartate
- Cholecystokinin

**Post-synaptic terminal**

- THC
- Dronabinol
- Nabilone

**Neurotransmitter receptor**

- Neurotransmitter emission
- Neurotransmitter reception

**Chemicals**

- Serotonin (5-HT)
- Glutamate
- Acetylcholine
- GABA
- Noradrenaline
- Dopamine
- D-aspartate
- Cholecystokinin

**Receptors**

- Neurotransmitter receptors

**Pathways**

- THC
- Dronabinol
- Nabilone

**Suppression of Neurotransmitter Release**

Health Canada 2016
Endogenous Cannabinoid System

Synthesis → Endocannabinoids → CB2 Receptor → CB1 Receptor → CBx Receptor → VR1 Receptor → Cellular uptake → Metabolism

Signal Transduction:

- Immune function
- Cell proliferation
- Inflammation
- Appetite
- Immune function
- Muscle control
- Pain
- IOP
- Cognition
- Emesis
- Neuroexcitability
- Reward
- Pain
- Vaso-dilation
- Pain
- Inflammation
- Thermoregulation
Cannabinoids and Pain

• Elevated levels of the CB1 receptor – like the opioid receptor – are found in areas of the brain that modulate nociceptive processing.

• CB1 and CB2 agonists have peripheral analgesic actions.

• CBs may also exert anti-inflammatory effects.

• Analgesic effects not blocked by opioid antagonists.

• Effective in rodent model of neuropathic pain.
Cannabis in painful HIV-associated sensory neuropathy  
A randomized placebo-controlled trial

D.I. Abrams, MD; C.A. Jay, MD; S.B. Shade, MPH; H. Vizoso, RN; H. Reda, BA; S. Press, BS; M.E. Kelly, MPH; M.C. Rowbotham, MD; and K.L. Petersen, MD

Abstract—Objective: To determine the effect of smoked cannabis on the neuropathic pain of HIV-associated sensory neuropathy and an experimental pain model. Methods: Prospective randomized placebo-controlled trial conducted in the inpatient General Clinical Research Center between May 2003 and May 2005 involving adults with painful HIV-associated sensory neuropathy. Patients were randomly assigned to smoke either cannabis (3.56% tetrahydrocannabinol) or identical placebo cigarettes with the cannabinoids extracted three times daily for 5 days. Primary outcome measures included ratings of chronic pain and the percentage achieving >30% reduction in pain intensity. Acute analgesic and anti-hyperalgesic effects of smoked cannabis were assessed using a cutaneous heat stimulation procedure and the heat/capsaicin sensitization model. Results: Fifty patients completed the entire trial. Smoked cannabis reduced daily pain by 34% (median reduction; IQR = -71, -16) vs 17% (IQR = -29, 8) with placebo (p = 0.03). Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group (p = 0.04). The first cannabis cigarette reduced chronic pain by a median of 72% vs 15% with placebo (p < 0.001). Cannabis reduced experimentally induced hyperalgesia to both brush and von Frey hair stimuli (p ≤ 0.05) but appeared to have little effect on the painfulness of noxious heat stimulation. No serious adverse events were reported. Conclusion: Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy. The findings are comparable to oral drugs used for chronic neuropathic pain.

NEUROLOGY 2007;68:515-521
Experimental Pain Model

Pain model timeline: Days 1 and 5

Time (min) -105 -95 -65 -60 -25 -15 0 15 25 55 65 95 105

LTS1 Forearm Heat Forearm Capsaicin VAS Map1 VAS2 RK1 Map2 LTS2 VAS4 RK2 Map3 LTS3 VAS5 RK3 Map4 LTS4 VAS6 RK4 Map5 LTS5

Smoke

Image of a forearm showing various pain model markers and VAS ratings.
Results: Neurology RCT

7-day Outpatient Pre-Intervention Phase
2-day Inpatient Lead-In Phase
5-day Inpatient Intervention Phase
7-day Outpatient Post-Intervention Phase

Placebo
Cannabis

hospital admission
first cigarette
last cigarette

Study Day

Abrams 2007
Results: Neurology RCT

Abrams 2007
Results: Neurology RCT

7-day Outpatient Pre-Intervention Phase

2-day Inpatient Lead-In Phase

5-day Inpatient Intervention Phase

7-day Outpatient Post-Intervention Phase

Study Day

-8 -7 -6 -5 -4 -3 -2 -1 1 2 3 4 5 6 7 8 9 10 11 12

Placebo
Cannabis

hospital admission
first cigarette
last cigarette

Abrams 2007
Results: Neurology RCT

Abrams 2007
Results: Neurology RCT

Abrams 2007
Results: Neurology RCT

- **Chronic Pain Intensity**
- **Painfulness of LTB**
- **% Change in Area of Secondary Hypersalgesia (brush)**
- **% Change in Area of Secondary Hypersalgesia (von Frey)**

Abrams 2007
NEURALGIC, Idiopathic
(Brown-Séquard)

Ext. Hyoscyamus .... 2-3 gr.
Ext. Conium .... 1-2 gr.
Ext. Ignatia .... 1-2 gr.
Ext. Opium .... 1-3 gr.
Ext. Aconite Leaves .... 1-4 gr.
Ext. Cannabis Ind. .... 1-5 gr.
Ext. Stramon. Seed .... 1-6 gr.
Ext. Bellad. Leaves ....

JOHN WYETH & BROTHER, Inc.
PHILADELPHIA

Guaranteed under The Food and
Drug Act, June 30, 1906.
Effects of cannabinoids in mice and rats

- THC enhances analgesic effect of morphine in a synergistic fashion
- Oral-Δ-9-THC increases potency of other mu opioids (hydromorphone and oxymorphone)
- Cannabinoids may enhance analgesic effect of opioids
  - The same analgesic effect may be achieved at lower opioid doses.
Cannabinoid–Opioid Interaction in Chronic Pain

DI Abrams¹, P Couey¹, SB Shade², ME Kelly¹ and NL Benowitz³

Cannabinoids and opioids share several pharmacologic properties and may act synergistically. The potential pharmacokinetics and the safety of the combination in humans are unknown. We therefore undertook a study to answer these questions. Twenty-one individuals with chronic pain, on a regimen of twice-daily doses of sustained-release morphine or oxycodone were enrolled in the study and admitted for a 5-day inpatient stay. Participants were asked to inhale vaporized cannabis in the evening of day 1, three times a day on days 2–4, and in the morning of day 5. Blood sampling was performed at 12-h intervals on days 1 and 5. The extent of chronic pain was also assessed daily. Pharmacokinetic investigations revealed no significant change in the area under the plasma concentration–time curves for either morphine or oxycodone after exposure to cannabis. Pain was significantly decreased (average 27%, 95% confidence interval (CI) 9, 46) after the addition of vaporized cannabis. We therefore concluded that vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects.

• Funded by the National Institute on Drug Abuse (NIDA)
• Published 2 November 2011 in Clinical Pharmacology & Therapeutics
Cannabinoid-Opioid Interaction Trial

Objectives

• Evaluate effects of vaporized cannabis on blood levels of prescribed opioids
• Sustained-release morphine
• Sustained-release oxycodone
• Determine the short-term side effects of co-administration of cannabis and opioids
• Assess effect of vaporized cannabis on level of chronic pain
## Participant Characteristics

<table>
<thead>
<tr>
<th>Morphine</th>
<th>Oxycodone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number Enrolled</td>
</tr>
<tr>
<td>10</td>
<td>Women</td>
</tr>
<tr>
<td>4</td>
<td>Caucasian</td>
</tr>
<tr>
<td>8</td>
<td>Age</td>
</tr>
<tr>
<td>42.9 (33-55)</td>
<td>Opioid Dose</td>
</tr>
<tr>
<td>62 mg bid (10-200)</td>
<td>Pain Score day 1</td>
</tr>
<tr>
<td>34.8 (29.4, 40.1)</td>
<td></td>
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</table>
Plasma Opiate Levels by Study Day

Morphine Group

Oxycodone Group

Cannabinoids did not significantly change the plasma level of opioids

Abrams 2011
# Pain by Study Day

<table>
<thead>
<tr>
<th></th>
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<th>Difference Mean (95% CI)*</th>
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<tr>
<td><strong>Overall</strong></td>
<td>21</td>
<td>39.6 (35.8, 43.3)</td>
<td>29.1 (25.4, 32.8)</td>
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<td>-11.2 (-16.5, -6.0)</td>
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<td><strong>Oxycodone</strong></td>
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<td>43.8 (38.6, 49.1)</td>
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*p<0.001

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32.1% reduction

Abrams 2011
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*p<0.001

- **Overall:** 32.1% reduction
- **Morphine:** 32.1% reduction
- **Oxycodone:** 23.5% reduction

Abrams 2011

[www.doh.dc.gov](http://www.doh.dc.gov)
Conclusions

Co-administration of vaporized cannabis with oral sustained-release opioids is safe.

Co-administration of vaporized cannabis trends towards lowering concentration of the opioids:
- The PK effects would be expected to reduce the analgesic effects of the opioids.
- The effect of vaporized cannabis to enhance opioid analgesia occurs by a pharmacodynamic, not a pharmacokinetic mechanism.

Co-administration of vaporized cannabis in subjects on stable dose of morphine or oxycodone appears to enhance analgesia.
POISON
No. 100
969
CHOCOLATE-COATED
TABLETS
CHLORODYNE
HALF STRENGTH
MORPH. HYDROCHL.
1-12 gr.
Ext. Cannabis 1-8 gr.
Nitroglycerin 1-600 gr.
Oleores. Capsc. 1-20 gr.
Peppermint Oil q. s.
Dose 1 to 4 Tablets

SHARP & DOHME
BALTIMORE
872196A

www.doh.dc.gov
Therapeutics

• In adults with chemotherapy-induced nausea and vomiting, oral cannabinoids are effective antiemetics.
• In adults with chronic pain, patients who were treated with cannabis or cannabinoids were more likely to experience a clinically significant reduction in pain symptoms.
• In adults with multiple sclerosis-related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.
• For these conditions, the effects of cannabinoids are modest; for all other conditions evaluated there is inadequate information to assess benefits.
# Fewer pills prescribed in medical pot states

Difference between annual drug doses prescribed per physician in medical marijuana states, and in states without medical marijuana laws, by drug category

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differential Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>1,826 fewer doses</td>
</tr>
<tr>
<td>Anxiety</td>
<td>562 fewer doses</td>
</tr>
<tr>
<td>Nausea</td>
<td>541 fewer doses</td>
</tr>
<tr>
<td>Psychosis</td>
<td>519 fewer doses</td>
</tr>
<tr>
<td>Seizures</td>
<td>486 fewer doses</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>362 fewer doses</td>
</tr>
<tr>
<td>Depression</td>
<td>265 fewer doses</td>
</tr>
<tr>
<td>Spasticity</td>
<td>32 fewer doses</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>35 more doses</td>
</tr>
</tbody>
</table>

Source: Bradford and Bradford, Health Affairs, July 2016
The Safety of Cannabis

• No overdose deaths have been reported.
• An estimated 800 cigarettes would be required to kill
  • Death would be from CO poisoning
• Unlike opioid receptors, dearth of brainstem cannabinoid receptors
• Addictive potential and minor withdrawal syndrome less than or equal to caffeine

Grothenherman 2002
Who Got Hooked

An Institute of Medicine study found dependency rates for marijuana were far lower than those for other substances.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent of General Population Who Had Ever Used</th>
<th>Percent of Those Users Who Ever Became Dependent on the Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>76%</td>
<td>32%</td>
</tr>
<tr>
<td>Heroin</td>
<td>2</td>
<td>23%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>16</td>
<td>17%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>92</td>
<td>15%</td>
</tr>
<tr>
<td>Anti-anxiety drugs</td>
<td>13</td>
<td>9%</td>
</tr>
<tr>
<td>Marijuana</td>
<td>46</td>
<td>9%</td>
</tr>
</tbody>
</table>
Cannabis and Pain: DC Experience

Mikhail Kogan, MD
Medical Director
GW Center for Integrative Medicine
Assistant Professor of Medicine
Associate Director of Geriatric and Integrative Medicine Fellowships
George Washington University
Conflicts of Interest

- Dr. Mikhail Kogan did not disclose any financial conflicts of interest.
- Dr. Kogan does recommend Medical Cannabis to patients in DC.
Case: Middle aged man with chemotherapy induced neuropathy

Patient

• 59 year old man survival of colon cancer treated with surgery and chemo.
• Severe Chemotherapy induced neuropathy for months. Tried number of medications with partial response and number of side effects.
• Primary care doctor and oncologist refused to recommend cannabis citing lack of evidence and not participating in DC Medical Cannabis program.
• Other symptoms: Weight loss, Poor appetite “food does not taste good”
• BMI on 1st visit 18.5

Goals
Control pain and gain some weight
Case: Middle aged man with chemotherapy induced neuropathy

Patient

- 59 year old man survival of colon cancer treated with surgery and chemo.
- Severe Chemotherapy induced neuropathy for months. Tried number of medications with partial response and number of side effects.
- Primary care doctor and oncologist refused to recommend cannabis citing lack of evidence and not participating in DC Medical Cannabis program.
- Other symptoms: Weight loss, Poor appetite “food does not taste good”
- BMI on 1st visit 18.5

Goals

Control pain and gain some weight

8 weeks after recommendation

- Gained 5 lbs, no side effects, reports use twice daily with vaporizer, pain is mostly controlled, occasionally needs to use extra few doses/day.
- Tolerating euphoria well and the only problem – COST but “it is worth it”
Clinical Side of Recommending Cannabis: Philosophy and Logistics
THC: Tetrahydrocannabinol
Beyond Psychoactive Effects

- Anti-emetic
- Anti-inflammatory
- Analgesic
CBD: Cannabidiol
Non Psychoactive cannabinoid

Non psychoactive, discovered in 1963

- Modulates THC effects, low affinity to CB1 and CB2 receptors
- Potent P450 3A11 inhibitor – blocking formation of most psychoactive metabolite of THC – 11-OH
- Sedative properties – reduces anxiety and other negative THC side effect
- Mild analgesic effects
- Anti-inflammatory
Figure 1. Pharmacological actions of non-psychoactive cannabinoids (with the indication of the proposed mechanisms of action). 
Abbreviations: Δ⁹-THC, Δ⁹-tetrahydrocannabinol; CB₁, cannabinoid CB₁ receptor; CBD, cannabidiol; Δ⁹-THCV, Δ⁹-tetrahydrocannabinolic acid; CBG, cannabinoid; CBDA, cannabidiolic acid; TRPV₁, transient receptor potential vanilloid type 1; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SARM, SARM receptor subtype 1A; FAAH, fatty acid amide hydrolase. (+), direct or indirect activation; (-), increase; (-), decrease.
A systematic review of 18 randomized controlled trials (RCTs) with a total of 766 participants with chronic non-cancer pain found that 15/18 trials showed a significant analgesic effect of cannabinoids, compared to placebo.

- No serious adverse events were reported.
A systematic review identified 28 studies (27 placebo-controlled, 1 treatment-controlled) of cannabis in a total of 2,454 participants with chronic pain.

- 12 studies of neuropathic pain
- 6 trials of other types of pain
- 3 for cancer pain
- 3 for diabetic neuropathy
- 2 for fibromyalgia
- 2 for HIV-associated sensory neuropathy

Preparations tested included nabiximols, nabilone, inhaled cannabis, THC (oral or oralmucosal), and dronabinol.

Studies generally showed improvements in pain measures with cannabis and cannabinoids.

Whiting 2015
## Chronic Pain Neuropathic Pain

<table>
<thead>
<tr>
<th>STUDY</th>
<th>POPULATION</th>
<th>TREATMENT</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams (2007)</td>
<td>RCT (parallel group) in 55 patients with HIV-associated neuropathy.</td>
<td>Smoked cannabis (3.56% THC) or placebo cigarettes without cannabinoids 3 times/day for 5 days.</td>
<td>Smoked cannabis reduced daily pain by 34% vs. 17% in placebo group (p=0.03); greater than 30% reduction in pain was reported by 52% in cannabis group vs. 24% in control (p=0.04). The first cigarette reduced chronic pain by 72% in cannabis group vs. 15% in control (p&lt;.001).</td>
</tr>
<tr>
<td>Ellis (2009)</td>
<td>RCT (crossover) in 34 patients with HIV-associated neuropathy.</td>
<td>Cannabis (1-8% THC) or placebo 4 times/day for 5 consecutive days/week for two weeks.</td>
<td>The proportion with pain reduction greater than 30% was 0.46 with cannabis vs. 0.18 with placebo; pain reduction was greater with cannabis than placebo (p=.016).</td>
</tr>
<tr>
<td>GW Pharma Ltd (2005)</td>
<td>RCT (parallel group) in 297 patients with diabetic peripheral neuropathy.</td>
<td>Nabiximols (Sativex) or placebo up to 24 sprays/day over 14 weeks.</td>
<td>There was no benefit of nabiximols over placebo in proportion of patients with pain reduction greater than 30%.</td>
</tr>
<tr>
<td>Selvarajah (2010)</td>
<td>RCT (parallel group) in 30 patients with diabetic peripheral neuropathy.</td>
<td>Nabiximols (Sativex) or placebo up to 4 sprays/day over 2 weeks.</td>
<td>There was no benefit of nabiximols over placebo on mean daily pain scores.</td>
</tr>
<tr>
<td>Wallace (2013)</td>
<td>RCT (crossover) in 16 patients with diabetic peripheral neuropathy.</td>
<td>Oromucosal spray (1%, 4%, and 7% THC) or placebo in single doses</td>
<td>There was a significant difference between placebo and all doses (p&lt;.05) for spontaneous pain. High doses were significantly better than low/medium doses (p=.001). Only high doses were effective for evoked pain (p&lt;.001).</td>
</tr>
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# Chronic Pain Neuropathic Pain

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<td>Berman (2007)</td>
<td>RCT (crossover) in 117 patients with central neuropathic pain (non-acute spinal cord injury). (unpublished abstract of conference presentation)</td>
<td>Nabiximols (Sativex) (2.7 mg THC and 2.5 mg CBD); THC spray, or placebo up to 48 sprays/24 h for 2 weeks each.</td>
<td>There was no difference between nabiximols (Sativex) and placebo for NRS pain scores.</td>
</tr>
<tr>
<td>Berman (2004)</td>
<td>RCT (crossover) in 48 patients with central neuropathic pain (brachial plexus avulsion)</td>
<td>Nabiximols (Sativex) (2.7 mg THC and 2.5 mg CBD); THC spray, or placebo up to 48 sprays/24 h for 2 weeks each.</td>
<td>Nabiximols (Sativex) was superior to placebo in reduction in pain score (by diary entry (p&lt;.005).</td>
</tr>
<tr>
<td>Frank (2008)</td>
<td>RCT (crossover) in 96 patients with mixed neuropathic pain</td>
<td>Dihydrocodeine (30mg-240mg) or nabilone (250 mcg-2mg) for 7 weeks each.</td>
<td>Dihydrocodeine was significantly better than nabilone as measured by the visual analogue score (VAS) (p=.01).</td>
</tr>
<tr>
<td>Karst (2003)</td>
<td>RCT (crossover) in 21 patients with chronic neuropathic pain</td>
<td>CT-3 (a synthetic cannabinoid) 20 mg orally or placebo 2x/day for 4 days, then 40 mg 2x/day for 3 days.</td>
<td>Treatment and placebo in pain measured by visual analog scale 3 hours after intake, but differences were less pronounced after 8 hours (p=.02).</td>
</tr>
<tr>
<td>Langford (2013)</td>
<td>RCT (parallel group) in 339 patients with central neuropathic pain due to MS</td>
<td>THC/CBD spray (2.7 mg THC and 2.5 mg CBD) or placebo, self-titrated for 14 weeks.</td>
<td>THC/CBD spray was not superior to placebo in mean NRS pain score.</td>
</tr>
<tr>
<td>Nurmikko (2007)</td>
<td>RCT (parallel) in 125 patients with neuropathic pain characterized by allostynia</td>
<td>Nabiximols spray (2.7 mg THC and 2.5 mg CBD) up to 48 sprays/24 h for 7-10 days.</td>
<td>Nabiximols (Sativex) was superior to placebo in mean reduction in pain intensity scores by VAS (p=.004)</td>
</tr>
</tbody>
</table>
Cannabinoids are effective for the treatment of pain, especially neuropathic pain.

Another systematic review and meta-analysis of 18 double blind randomized placebo-controlled trials of cannabis and cannabinoid treatments for chronic pain also showed that cannabis and cannabinoids appear to reduce pain intensity.

Martin-Sanchez 2009

6 double-blind randomized controlled trials (n=226) studied the use of medical cannabis in neuropathic pain. All studies showed a statistically significant benefit in terms of pain relief.

Deshpande 2015
Case: Peripheral Neuropathy in Elderly Woman

**Patient**
- 76 year old frail woman with diabetes-related peripheral neuropathy and chronic kidney disease admitted to the hospital ICU with severe delirium.
- 7 days before admission, gabapentin dose was increased to 300mg every 8 hours.
- Geriatrics consult was called. Gabapentin was rapidly tapered down and delirium slowly resolved.

**Outpatient treatment**
- Weekly acupuncture
- Finished gabapentin taper
- Combination of alpha-lipoic acid, benfotiamine, and GLA (evening primrose oil)
- Medical cannabis recommendation – sublingual tincture as needed
“Well I did get very high a few times, reminded me of my hippie years. After few weeks I figured out how to dose it just right.”

“I have no idea if supplements are doing anything but acupuncture has been somewhat helpful.”

“I have to choose pot over acupuncture, all these costs add up.”

“Can’t you write me some letter for Medicare? I mean why all your effective treatments are not covered, while the medication that almost killed me is?”

“Oh, and my primary care doctor wants you to call him. He thinks I should not use pot as it is very dangerous at my age and he wants to put me on another medication instead, but I don’t think so.”
Cannabis Toxicity/Addiction

Active/Lethal Dose Ratio and Dependence Potential of Psychoactive Drugs

Legend:
- Narcotics
- Depressants
- Stimulants
- Anesthetics
- Hallucinogens
- Cannabis

Gable 2006
Cannabis Toxicity/Addiction

Active/Lethal Dose Ratio and Dependence Potential of Psychoactive Drugs

- Very high
- High
- Moderate / High
- Moderate
- Moderate / Low
- Low
- Very low

Legend:
- Narcotics
- Depressants
- Stimulants
- Anesthetics
- Hallucinogens
- Cannabis

Gable 2006
Acute Pain

RCTs have shown:

- No effect of intravenous THC on dental extraction pain. *Raft 1977*
- No effect of THC capsules or sublingual spray on post-operative pain after abdominal hysterectomy. *Buggy 2003*
- Levonantradol* was shown to be no more effective than codeine for acute post-operative pain. *Campbell 2001*
  
  *Levonantradol is a synthetic, potent analog of THC, usually given intramuscularly. Levonantradol is no longer used clinically.*

Cannabis and cannabinoids are not recommended for acute pain.
Administration and Formulations

Inhalation by smoking or vaporization
(herbal cannabis, resin, concentrates)

Inhalation by smoking or vaporization
(prescription cannabinoids, edibles, tinctures)

Oral or sublingual
(lollipops, lozenges, nabiximols)

Topical or Rectal
(herbal cannabis, resin, concentrates)
Cannabis vs. Cannabinoids

Advantages of cannabis
• Many clinicians believe cannabis has a different effect than synthesized cannabinoids.
• Cannabis has many different cannabinoid and non-cannabinoid constituents that may work synergistically (the so-called “entourage effect”).
• Cannabis is less expensive than prescription forms.
• It is much easier to slowly and precisely titrate the dose.
• Typically there are fewer side effects, mostly due to the presence of CBD and avoiding oral administration.

Advantages of cannabinoids
• High quality control
• No variability between batches
• Possibly insurance coverage

For both cannabis and cannabinoids, “Start low and go slow.”
Smoking

• A “joint” contains 0.5 - 0.8 g of cannabis with about 4 - 8% THC, but many strains now are much stronger.
  • About 20 - 70% of that ~ 5 mg of THC reaches the lungs
  • About 30% of THC and CBD is bioavailable
• Plasma peaks of THC occur in 3 to 10 minutes.
• Plasma clears in about 3 hours, the high usually lasts about 1 to 2 hours, sometimes up to 4 hours.

The Pot Book 2010
Vaporizing

Pros

• Much lower temperature
• Minimal particulate matter
• Less carbon monoxide
• Better THC delivery compared to smoking due to loss of THC at high temperature
• Lower risk of accidental burn injuries or fires
• Some are easy to use (pen oil vaporizers)

Cons

• Need special equipment
• Higher cost (ranges from $50 - 500)
• Some more difficult to use
• Long term risks of inhaling vaporized oils are unknown
Oral and Sublingual Use of Whole Plant Extracts

- Oral administration
  - Slow peak level and prolonged psychoactive effect
  - No seizures or CNS suppression due to CBD counter effect at cannabinoid receptors, in contrast to pure THC products

- Oil and whole plant tinctures available for oral and sublingual use
  - Some are very potent
  - Per mg cost of active ingredients is often cheaper
  - Often more stable
  - Some commercial products have very high CBD:THC ratio and have minimal or no psychoactive effects
  - In my experience, 8:1 CBD:THC ratio does not caused psychoactive side effects
Case – Young patient with chronic facial pain

Patient
• 21 year old healthy college student on soccer scholarship
• Head trauma with loss of teeth and oral fractures during soccer
• Multiple oral and dental surgeries
• Referred by oral surgeon

On presentation to the clinic
• Severe facial pain mostly in lower jaw, upper neck, and headaches
• Frequent and severe flares, responding best to intravenous ketamine infusion when admitted to the hospital. At times pain-free between flares.
• OxyContin and OxyIR with typical total oxycodone daily dose 120-150mg/day
• Sleep disrupted, anxiety, and depression with suicidal thoughts, weight gain of 30 lbs., craving sweets and alcohol
• Unable to exercise or play soccer, dropped out of college, moved back in with his parents
Case – Young patient with chronic facial pain

**Treatment plan**

- Working with psychiatrist: antidepressant, mood stabilizer, weekly cognitive behavioral therapy (CBT), breathing and mindfulness practices
- Anti-inflammatory diet, fish oil, methylated B complex
- Acupuncture
- Gradual exercise and manual medicine with PT
- Twice a month low dose intravenous ketamine infusions
- Inhaled high-THC preparation as needed throughout the day and scheduled sublingual tincture of cannabis (1:1 THC:CBD ratio) whole plant extract at bedtime
Case Progression

3 MO.

- Down to oxycodone 10 mg as needed, 30 tabs (used only during flares) lasted 2-3 months
- Decreased ketamine infusions frequently, stopped acupuncture

6 MO. +1

- Lost 30 lbs. of gained weight, slowly increased exercise (mostly walking and swimming)
- Depression lifted, started to taper off antidepressants
- Stopped all inhaled cannabis, occasionally uses sublingual tincture for sleep or for flares
Qualifying Medical Conditions

In early years of law:
HIV-related cachexia, glaucoma, MS-relate spasticity, side effects from cancer treatments

Now:
Up to recommending physician to determine if patient has qualifying medical condition

Who can recommend?
• DOs
• MDs
• NDs (recently added)
GOVERNMENT OF THE DISTRICT OF COLUMBIA
Department of Health
Division of Medical Marijuana and Integrative Therapy

Patient Information

First Name * 
Middle Initial 
Last Name * 
Date of Birth * 

Street * 
Apt/Suite 
City * 
State * 
Zip * 

Phone Number * 
ext. 

Email Address 

Diagnosis * 

Physician Information

First Name 
mkhall
Middle Initial 

Last Name * 
kogan

Business Street 
908 New Hampshire Ave 

Business Apt/Suite 
200 

Business City 
washington 

Business State 
DC 

Business Zip 
20037 

Specialty/area of clinical practice 
internal medicine, geriatrics, palliative medicine 

DC Medical License Number 
md036716 

Length of time Physician rec has been under physician care * 

ATTESTATION FORM

Physicians in accordance with DCMR §22C-800.1-801, I hereby certify that:
- I am a physician who is licensed in good standing to practice medicine or osteopathy in the District of Columbia.
- I have a bona fide physician-patient relationship with the qualifying patient.
- I have completed a full assessment of the patient’s medical history and current medical condition, including a personal physical examination, not more than ninety (90) days prior to making the recommendation.
- The patient has a qualifying medical condition or suffers from the side effects of a qualifying medical treatment.
- In my professional opinion, the potential benefits of the medical use of marijuana would likely outweigh the health risks for the patient.
- I have responsibility for the ongoing care and treatment of the patient, provided that such ongoing treatment shall not be limited to or for the primary purpose of the provision of medical marijuana use or consultation solely for that purpose.
- I have made the recommendation for medical marijuana based upon my assessment of the patient’s medical history, current medical condition, and a review of other approved medications and treatments that might provide the patient with relief from the condition or the side effects of its treatment.
- I do not have a professional office located at a dispensary or cultivation center or receive financial compensation from a dispensary or cultivation center.

DCMR §22C-801.1(g): I have explained the potential risks and benefits of the use of marijuana to the qualifying patient and the qualifying patient’s parent or legal guardian, if applicable.

Physician’s Name * 

Date * 

Physician’s DOB * 

Physician’s Last 4 SSN *
What Recommenders Need to Know

• How to counsel patients about risks and benefits
• How to pick the right strain
• Appropriate ratios of THC:CBD
• Effects of other cannabinoids
• What are the routes of administration I should suggest?
• How much can I rely on a medical cannabis dispensary to educate my patients?
Resources

For more information on prescribing in the District and to become a recommending physician visit:

doh.dc.gov/mmp

Please visit DCRx for a full list of references and more information on these and other treatment-related subjects.

doh.dc.gov/dcrx

Questions can be sent by email to
doh.mmp@dc.gov or by regular mail to:

Medical Marijuana Program
Health Regulation and Licensing Administration
899 N. Capitol Street, NE
2nd Floor
Washington, DC 20002
Audience Questions
Do you have any experience recommending cannabis for patients who are weaning off opioids?
Does cannabis work for all types of chronic pain, i.e. back pain, fibromyalgia, arthritis?
Is there any difference in reimbursement between California and DC?
How do you treat chronic pain patients who are also being treated with antipsychotics, antidepressants, or mood stabilizers?
Would you recommend cannabis for pregnant patients dealing with chronic pain?
Do you recommend cannabis to patients who have a history of addiction or substance use disorder?
More resources available at the DC Center for Rational Prescribing
doh.dc.gov/dcrx
DCRx Modules

- Tight Control in Type 2 Diabetes: More Harm Than Good?
- Taking a Sexual History to Reduce HIV Risk
- Myths and Facts about Opioids
- Medical Cannabis: An Introduction to the Biochemistry & Pharmacology
- Medical Cannabis: Evidence on Efficacy
- Medical Cannabis: Adverse Effects and Drug Interactions
- Industry Influence on the Practice of Medicine
- What You Need to Know about PrEP
- Getting Patients Off of Opioids
- Rational Prescribing in Older Adults
- Drug Approval and Promotion in the United States
- Generic Drugs: Myths and Facts

www.doh.dc.gov