THE USE OF CANNABIS IN PALLIATIVE CARE PATIENTS

“Crossroads Of Marijuana: Do It Right”
Oklahoma State Medical Association
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DISCLOSURES / CONFLICTS OF INTEREST

• None
LEARNING OUTCOMES

1. Review the history of the use of cannabis in medicine
2. Describe the primary pharmacological actions of exogenous cannabinoids, via endocannabinoid system receptor modulation
3. Review key practical recommendations on the integration of cannabinoids for symptom management in palliative care patients
• Wind-pollinated
• Two sexes (occ. hermaphrodites)
• ~38 million years old
• UV exposure in Himalayas
• Domesticated ~18,000 years ago
• Protection of traditional medical knowledge
• Aid in spiritual development
  • Remains consecrated

• In 19th century: sold by Merck in Germany, Bourroughs, Wellcome & Co. in the UK, and Squibb, Parke, Davis & Co., and Eli Lilly & Co. in the USA
CANNABINOIDS AND OPIOIDS: AN HISTORICAL PERSPECTIVE

**Cannabinoids**

- **500 BC**: Earliest known reference for opium-based elixir
- **1522**: W.B. O'Shaughnessy's work popularizes cannabis use in India
- **1804**: Medicinal cannabis use declines
- **1817**: Paracelsus reference to "laudanum", opium-based elixir, as a potent painkiller
- **1900's**: 9-THC identified as main psychoactive agent in Cannabis sativa plant
- **1988**: CB1 receptor identified.
- **1998**: Endogenous cannabinoid ligands shown to be analgesic

**Opioids**

- **500 BC**: Earliest known reference for opium-based elixir
- **1522**: W.B. O'Shaughnessy's work popularizes cannabis use in India
- **1804**: Morphine extracted from opium poppy plant
- **1817**: Morphine first marketed in Germany as analgesic
- **1874**: Morphine analogs synthesized: 1874: Diacetylmorphine (heroin) 1900s: codeine, dihydromorphine, oxycodone, pethidine, oxymorphone
- **1900's**: Morphine analogs synthesized: 1874: Diacetylmorphine (heroin) 1900s: codeine, dihydromorphine, oxycodone, pethidine, oxymorphone
- **1970s**: Discovery of opioid receptors – µ (mu), κ (kappa), δ (delta)
- **1975**: Discovery of endogenous opioid peptides - endorphins

Slide courtesy of M. Ware

pubmed - cannabis OR cannabinoid OR endocannabinoid
Sir Dr. W.B. O'Shaughnessy (1809-1889)

- First to describe IV electrolyte hydration to treat cholera victims
- Knighted for laying telegraph lines in India
- Introduced Cannabis to Western Medicine, learning from Calcuttans

Presented in October 1839: a treatise on cannabis which showed the apparent utility of a locally produced plant extract in Kolkata administered to patients suffering from rabies, cholera, tetanus, infantile convulsions, and painful rheumatological conditions (later, FRS)

ON THE PREPARATIONS OF THE INDIAN HEMP, OR GUNJAH (CANNABIS INDICA); THEIR EFFECTS ON THE ANIMAL SYSTEM IN HEALTH, AND THEIR UTILITY IN THE TREATMENT OF TETANUS AND OTHER CONVULSIVE DISEASES

Transactions of the Medical and Physical Society of Bengal 8, 1838-40, 462-469.

Assistant-Surgeon, and Professor of Chemistry, In the Medical College of Calcutta.
November 22, 1838
Kolkata, India
use of cannabis to treat Hakim Abdullah, who had been bitten by a rabid dog 3 weeks prior

pulse 125
skin: cold and moist
left forearm: small red and painful cicatrix
unable to swallow liquid or quench thirst -- every attempt to swallow water or trickle drips on tongue led to severe paroxysms...
"Two grains of Hemp resin in a soft pillular mass were ordered every hour"

after the third dose..." He talked calmly of drinking, but said it was in vain to try -- but he could suck an orange; this was brought to him, and he succeeded in swallowing the juice without any difficulty.

The Hemp was continued till the sixth dose, when he fell asleep and had some hours' rest.

The Hemp was again repeated, and again by the third dose the cheering alleviation of the previous day was witnessed. He ate a piece of sugar-cane, and again swallowed the juice - he partook freely of some moistened rice, and permitted a purgative enema to be administered.

His pulse was nearly natural, the skin natural in every respect. His countenance was happy. On one subject only was he incoherent, and even here was manifested the powerful and peculiar influence of the narcotic. He spoke in raptures of the inmates of his zenana and his anxiety to be with them. We ascertained however that he had no such establishment.
Four days thus passed away, the doses of Hemp being continued. When he fell asleep, on waking the paroxysms returned, but were again almost immediately assuaged as at first. Meanwhile purgative enemata were employed, and he partook freely of solid food, and once drank water without the least suffering. But about 3 P.M. of the fifth day he sunk into profound stupor, the breathing slightly stertorous; in this state he continued, and without further struggle, death terminated his sufferings at 4 A.M. of the 27th November.

It seems evident that at least one advantage was gained from the use of the remedy - the awful malady was stripped of its horrors; if not less fatal than before, it was reduced to less than the scale of suffering which precedes death from most ordinary diseases.... Next to cure, the physician will perhaps esteem the means which enable him "to strew the path to the tomb with flowers," and to divest of its specific terrors the most dreadful malady to which mankind is exposed.

O'Shaughnessy WB. On the preparations of the Indian hemp, or gunjah (Cannabis indica); their effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases. Trans Med Phys Soc Bengal 1838-1840; 71-102:421-461.
Sir Dr. William Osler (1849-1919)

- Founder of Johns Hopkins Hospital
- Created the first residency program
- Described as the "Father of Modern Medicine"
Sir Dr. William Gowers (1845-1915)

- Started checking hemoglobin levels
- Introduced ophthalmoscope as essential tool in examination
- Described by a President of World Federation of Neurology as "probably the greatest clinical neurologist of all time"
Sir Dr. J. Russell Reynolds (1828-1896)

Queen Victoria’s personal physician for 37 years
President of the Royal College of Physicians & British Medical Association
First to distinguish pure epilepsy syndrome

"When pure and administered carefully, it is one of the most valuable medicines we possess."
Interestingly, over 125 years ago, the debate about when cannabis versus opioids was appropriate for pain treatment appeared in medical journals.

“With a wish for speedy effect, it is so easy to use that modern mischief-maker, hypodermic morphia, that they [young physicians] are prone to forget results of incautious opiate giving. Would that the wisdom that has come to their professional fathers through, it may be, a hapless experience, might serve them to steer clear of narcotic shoals on which many a patient has gone awreck. Indian hemp is not here lauded as a specific. It will, at times, fail. So do other drugs. But the many cases in which it acts well, entitle it to a large and lasting confidence. My experience warrants this statement: cannabis indica is, often, a safe and successful anodyne and hypnotic”

Mattison was medical director of Brooklyn Home for Narcotic Inebriates and was the first person to carry out large-scale “pharmacovigilance” study of cocaine, reporting in 1887.
Considered the single greatest experimental scientist of the seventeenth century (Biotechnology 101)
The Nobel Prize in Physiology or Medicine 1970 was awarded jointly to Sir Bernard Katz, Ulf von Euler and Julius Axelrod "for their discoveries concerning the humoral transmitters in the nerve terminals and the mechanism for their storage, release and inactivation".

Dr. Julius Axelrod (1912-2004)
Cannabinoid Signaling Science

- Last decade of 20th Century
- New field of biology & physiology
- 600 million years in life
- Found even in sea squirts & hydra
- Going on all the time in many tissues and organ systems
  - Spleen, gut, skin, & immune cells
  - Brain, heart, gonads
- Major ramifications for health
Cannabinoid Receptors

- G-protein–coupled receptors
- CB₁ receptors highly expressed in the brain
  - CB₁ receptors also found in adipose tissue, liver, muscle, the gastrointestinal tract, pancreas, as well as reproductive and cardiovascular tissues
- CB₂ receptors are expressed primarily in immune cells
  - CB₂ receptor expression in neurons is being studied

AEA also an endovanilloid at TRPV1
(with 5-20-fold lower affinity cf with CB1); also PPARγ

**Cannabinoid receptors are G-protein-coupled receptors**

**Endocannabinoids**

- Anandamide
- 2-Arachidonoyl-glycerol

Endogenous, phospholipid-derived metabolites that bind to and activate cannabinoid receptors


**Key ECS Elements**

- **Central nervous system**
  - Hippocampus
  - Basal ganglia
  - Cortex
  - Cerebellum
  - Hypothalamus
  - Limbic structures
  - Brainstem

- **GI tract (myenteric neurons and epithelial cells)**
- **Liver (hepatocytes)**
- **Adipose tissue**
- **Muscle**
- **Pancreas (α-cells)**

- **Immune cells and tissues**
  - T cells, B cells
  - Macrophages
  - Dendritic cells
  - Spleen, tonsils
  - Adipose tissue
Activation → negatively coupled to adenylate cyclase, suppresses neuronal Ca^{2+} conductance, inhibits inward rectifying K^{+} conductance → suppression of neuronal excitability

The CB_1 receptor consists of 7 transmembrane helices

Courtesy of Patricia Reggio, PhD
GLOBAL STRUCTURE OF CB1 BOUND TO TARANABANT

DOCKING OF RIMONABANT AND THC TO THE CB1 RECEPTOR

Difference Between Classical and Retrograde Neurotransmission

Classical neurotransmitter

Presynaptic

Postsynaptic

Retrograde neurotransmitter

Presynaptic

Postsynaptic

Autoradiographic distribution of bound [18F]MK-9470 in the rhesus brain.
The CB1R is one of the most abundant G protein-coupled receptors in the CNS, rivaling the abundance of benzodiazepine, striatal dopamine, and ionotropic glutamate receptors (14), and is 10-fold higher than that of opioid receptors (26).
Physiological Effects of Endocannabinoids

- Endocannabinoids are often produced as an adaptive response to cellular stress, aimed at reestablishing cell homeostasis
- Endocannabinoids affect a large number of physiologic processes including
  - Feeding behavior
  - Energy balance, metabolism, and GI function
  - Pain perception
  - Motor control and posture
  - Learning, memory, and emotions
  - Immune and inflammatory responses
  - Cardiovascular function
  - Reproduction
  - Bone formation

Endocannabinoid signaling regulates

- mood,
- appetite,
- memory,
- inflammation,
- pain perception,
- muscle tone and movement,
- extinction of traumatic memories,
- protection of nerves & brain tissue,
- bone growth,
- tumor regulation,
- baby breastfeeding reward,
- stress management,
- eye pressure,
- gastrointestinal motility,
- seizure activity,
- and other areas of health
CBRS LOCALIZE TO PAIN PROCESSING AREAS

CB1
- Periaqueductal gray
- Rostral ventromedial medulla (nucleus raphe magnus -- antinociceptive actions of cannabinoids within RVM are primarily due to presynaptic inhibition of GABAergic neurotransmission)
- Thalamus
- Dorsal root ganglion
- Amygdala
- Cortex

CB2
- Immune cells, including microglia -- cytokine, chemokine modulation
- Dorsal root ganglion
- Brainstem
- Thalamus
- Periaqueductal gray
- Cerebellum

Clinical Endocannabinoid Deficiency Syndrome
CANNABINOID SUPPRESSION OF NEUROPATHIC PAIN – BASIC SCIENCE

Cannabinoids suppress neuropathic nociception in at least 9 different animal models of surgically-induced traumatic nerve or nervous system injury\(^1\):

- Chronic constriction injury: infraorbital nerve, saphenous nerve
- Partial nerve ligation: sciatic, saphenous
- Spinal nerve ligation: L5
- Spared nerve injury
- Spinal cord injury
- Tibial nerve injury
- Streptozotocin-induced diabetic neuropathy

\(^1\)Rahn EJ and Hohmann AG. Canabinoids as Pharmacotherapies for Neuropathic Pain: From the Bench to the Bedside. *Neurotherapeutics* 2009. 7:4, 713-737.
CANNABINOID SUPPRESSION OF NEUROPATHIC PAIN – BASIC SCIENCE

• CCI infraorbital nerve model: CB1↑ in ipsilateral and contralateral superficial layer of the trigeminal caudal nucleus (I>C)

• CB2 immunoreactivity↑ in ipsilateral dorsal horn s/p L5 spinal n. xsection

• Saphenous partial nerve ligation↑ u-opioid, CB1, and CB2 protein levels in ipsilateral/contralateral hind paw skin, DRG, & ipsilateral/contralateral L-cord (1-7 days post-surgery)

• Tibial nerve injury → CB1 mRNA in contralateral thalamus in 1 day

• SCI model—mechanical allodynia↓ with chronic WIN (mixed CB agonist), with no decrease in effectiveness, unlike morphine

1Rahn EJ and Hohmann AG. Canabinoids as Pharmacotherapies for Neuropathic Pain: From the Bench to the Bedside. Neurotherapeutics 2009. 7:4, 713-737.
Cannabinoid type 1 receptors on neurons in the medullary nucleus solitarius, part of the emesis circuit—chemoreceptor trigger zone

Cannabinoid inhibition of 5-HT3 receptor activity in this region—increased GABAergic activity

Receptor-independent pathways too
- ECS is like a symphony conductor
  - Homeostasis & equilibrium
  - Tens of thousands of papers

- >8,000 human subjects in published controlled clinical trials w/ cannabis & cannabinoids (RCTs in 50+ indications)

- About 140 controlled clinical studies with single cannabinoids, oral cannabis extracts and inhaled cannabis flowers have been conducted over the past 40 years.

- Compounds from Cannabis resin
  - Target specific receptors
  - Or indirectly increase system activity
  - Treat symptoms: chronic pain, anxiety, depressed mood, nausea, loss of appetite, spasms
  - Tamping down inflammation, reduction of toxicity from excess neurotransmitter release, quieting of seizures

- Exciting possibilities: controlling cancers, fighting infections & diabetes, psychological distress
- Cannabinoid science explains why cannabis resin has therapeutic utilities known for centuries

- Use of Cannabis in the preservation, promotion, and restoration of health scientifically sound

- Need more research on what types, how much, for which, for what conditions, desires, & individual chemistries

- Cannabinoid health science has been playing role in evolution of life predating birth of Cannabis

- Cannabis resin: organic, herbal, renewable, therapeutic cannabinoid delivery vehicle
Cannabinergic Pain Medicine
A Concise Clinical Primer and Survey of Randomized-controlled Trial Results

Sunit K. Aggarwal, MD, PhD
PubMed Survey of cannabinoid medicine RCTs: 56 hits, 38 RCTs met criteria. 71% (27) + cannabinoids had empirically demonstrable and statistically significant pain-relieving effects, 29% (11) - did not.

11 negative outcome RCTs: 3 investigated postoperative pain, 3 experimentally induced pain in healthy volunteers, 1 neuropathic pain in spinal cord injury, 2 pain in multiple sclerosis, 1 central neuropathic pain in brachial plexus avulsion, and 1 painful diabetic peripheral neuropathy.

<table>
<thead>
<tr>
<th>TABLE 2.</th>
<th>Descriptors of Pain Syndromes Investigated in Positive Outcome Randomized-controlled Trials of Cannabinoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimentally induced pain in healthy volunteers</td>
<td>Chronic pain in rheumatoid arthritis</td>
</tr>
<tr>
<td>Unspecified chronic noncancer pain</td>
<td>Chronic pain in multiple sclerosis</td>
</tr>
<tr>
<td>Chronic pain secondary to chronic upper motor neuron syndrome</td>
<td>Chronic neuropathic pain with hyperalgesia and allodynia</td>
</tr>
<tr>
<td>Cancer-related pain</td>
<td>Chronic neuropathic pain related to HIV, trauma, surgery, and CRPS</td>
</tr>
<tr>
<td>Chronic pain in fibromyalgia</td>
<td>CRPS indicates complex regional pain syndrome; HIV, human immunodeficiency syndrome.</td>
</tr>
</tbody>
</table>
The Health Effects of Cannabis and Cannabinoids: Current State of Evidence and Recommendations for Research

- January 2017: National Academies report published
- Washington State Department of Health was a Study sponsor
- Considered more than 10,000 scientific abstracts
- For clinical queries: only analyzed recent good- or fair-quality systematic reviews
- Found conclusive or substantial evidence that cannabis can effectively treat chronic pain, chemotherapy-induced nausea and spasticity.
- No evidence of cannabis overdose deaths.

- “In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms…the use of cannabis for the treatment of pain is supported by well-controlled clinical trials”

CONCLUSION 4-1 There is substantial evidence that cannabis is an effective treatment for chronic pain in adults.

Biologically plausible (not reviewed in NAS report): Potential analgesic sites of action for cannabinoids have been identified at brain, spinal cord, and peripheral levels…data indicate descending pain modulation pathway neurons in the rostroventral medulla and periaqueductal gray substance are involved in the brain-mediated analgesic effects of cannabinoids…spinal mechanisms…including cannabinergetic inhibition of g-aminobutyric acid, glycine, and glutamate release (PM&R 2014 6:363-72)
Until recent years, the vast majority of chemovars in Europe and North America were THC-predominant (Type I cannabis). Contemporaneously, there has been greater interest in mixed THC:CBD (Type II) and CBD-predominant (Type III cannabis) chemovars with broader mechanisms of action and improved therapeutic indexes.
FDA-Regulated Cannabinoid-Based Medicines:
Chemicals, Extracts, Botanicals

Dronabinol (Marinol™)

Nabilone (Cesamet™)

Cannabis Sativa L. Extracts (Sativex™)

Cannabis Sativa L. Cigarettes

Approximately 460 chemical constituents, >100 phytocannabinoids

1985 1985 2006 1976
CANNABIS PHARMACODYNAMICS

- THC
  - primary psychoactive component of cannabis
  - weak partial agonist on CB₁ and CB₂ receptors
  - effects on pain, appetite, digestion, emotions and thought processes
  - applicable for many symptoms and conditions including; pain, nausea, spasticity/spasms, appetite stimulation, anxiety, depression, post-traumatic stress disorder (PTSD), insomnia et al.

- CBD
  - has little affinity for CB₁ and CB₂ receptors directly
  - negative allosteric modulator of CB₁
  - pharmacological effects on various other receptor systems including TRPV1, 5-HT₁A, adenosine A2A and non-receptor mechanisms
  - analgesic, anti-inflammatory, anti-anxiety, and anti-psychotic, anticonvulsant, neuroprotectant, and anti-inflammatory (including autoimmune conditions

MacCallum and Russo. Practical considerations in medical cannabis administration and dosing. European Journal of Internal Medicine, March 2018, Volume 49, Pages 12–19
CANNABIS PHARMACOKINETICS

Herbal cannabinoid drug containing approximately six dozen different *phytocannabinoids* (terpenophenolics with a 21-carbon molecular scaffold) – 1000s of chemovars terpenoids, flavonoids, and phytosterols

THC acid and CBD acid: THC-predominant (Type I cannabis, mixed THC:CBD (Type II) and CBD-predominant (Type III cannabis)

Terpenes: myrcene (analgesic, sedating), limonene (antidepressant and immune-stimulating), pinene (AChE inhibitor, alleviating short-term memory impairment from THC), beta-caryophyllene (anti-inflammatory analgesic and selective full agonist at the CB$_2$ receptor).

5 minutes of heating at 200-210°C has been determined as the optimal conditions for maximal decarboxylation only a few seconds with a flame (> 600°C)
PK: COMMON ROUTES OF ADMINISTRATION

Lungs by inhalation of vaporized or smoked organic plant material
  Akin to “IV bolus”—passive diffusion
  Rapid onset (secs to mins), maximal effect ~30mins, duration 2-3 hrs
Gut by ingestion of lipophilic, alcoholic, or supercritical fluidic extracts
  More variable absorption time
  Onset 30mins-2hrs, more constant duration of action of 5-8hrs
Skin by topical application of extracts
## ADMINISTRATION FACTORS IN CANNABIS DELIVERY METHODS

<table>
<thead>
<tr>
<th>Issue</th>
<th>Smoking/vaporisation</th>
<th>Oral</th>
<th>Oromucosal</th>
<th>Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset (min)</td>
<td>5–10</td>
<td>60–180</td>
<td>15–45</td>
<td>Variable</td>
</tr>
<tr>
<td>Duration (h)</td>
<td>2–4</td>
<td>6–8</td>
<td>6–8</td>
<td>Variable</td>
</tr>
<tr>
<td>Pro</td>
<td>Rapid action, advantage for acute or episodic symptoms (nausea/pain)</td>
<td>Less odor, convenient and discrete, advantage for chronic disease/symptoms</td>
<td>Pharmaceutical form (nabiximols) available, with documented efficacy and safety.</td>
<td>Less systemic effect, good for localised symptoms</td>
</tr>
<tr>
<td>Con</td>
<td>Dexterity required, vaporisers may be expensive, and not all are portable</td>
<td>Titration challenges due to delayed onset</td>
<td>Expensive, spotty availability</td>
<td>Only local effects</td>
</tr>
</tbody>
</table>

MacCallum and Russo. Practical considerations in medical cannabis administration and dosing. European Journal of Internal Medicine, March 2018, Volume 49, Pages 12–19
Vaporization as a Smokeless Cannabis Delivery System: A Pilot Study

DI Abrams¹,²,³, HP Vizoso¹,², SB Shade¹,², C Jay⁴,⁵, ME Kelly¹,²,³ and NL Benowitz³,⁶

Slide courtesy of M. Ware.
PK: METABOLISM

- 95-99% THC is plasma protein bound (lipoproteins)
- Hydroxylation, oxidation, and conjugation (CYP2C9 and CYP3A)
- Rapidly cleared from plasma (70% tissues / 30% metabolized)
- First-pass metabolism with oral admin. (11-OH-THC)
- Elimination over several days (adipose)
- Breastmilk distribution
- Pregnancy Category C
- Excretion: days to weeks
  - 20-35% found in urine
  - 65-80% found in feces
  - 5% as unchanged drug (when given PO)
CONTRAINDICATIONS

Rare hypersensitivity to THC or allergies to any inert materials in formulations
Should be used with caution in patients with infection requiring Th1 immunity activity for inhibition (e.g., Legionella)
Should be used cautiously when personal or family history of psychosis

use with caution in unstable cardiac conditions, such as angina, due to tachycardia and possible hypotension due to THC, but produces no QTc issues

Controversial areas: use in pregnancy/lactation, children/teens, and in addiction/dependency
# ADVERSE EVENTS ASSOCIATED WITH CANNABIS-BASED MEDICINES

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Most common</th>
<th>Common</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness/fatigue</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough, phlegm, bronchitis (Smoking only)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive effects</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euphoria</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Toxic psychosis/paranoia</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ataxia/dyscoordination</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Tachycardia (after titration)</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Cannabis hyperemesis</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
When THC co-administered with CBD, as can occur with the usage of some strains of herbal cannabinoid medicines and certain cannabinoid-based extractions, anxiogenic, dysphoric, and possibly short-term memory interrupting effects of THC are mitigated.

Evidence suggests cannabinoid drugs can enhance the analgesic activity of co-administered opioids. Opioid dose reductions...
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.

Table 1  Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>Morphine group</th>
<th>Oxycodone group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Women</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Caucasian</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>42.9 (33–55)</td>
<td>47.1 (28–61)</td>
</tr>
<tr>
<td>Mean opioid dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mg) (range)</td>
<td>62 Twice daily (10–200)</td>
<td>53 Twice daily (10–120)</td>
</tr>
<tr>
<td>Mean pain score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>day 1 (95% CI)</td>
<td>54.8 (29.4, 40.1)</td>
<td>43.8 (38.6, 49.1)</td>
</tr>
</tbody>
</table>

CI, confidence interval.
Cannabinoid:Opioid Interaction Trial: Design

- 5-day inpatient study in Clinical Research Center at SFGH
- 12-hour blood sampling on day 1 on stable daily dose of opioid analgesic
- Vaporization of 3.2% THC cannabis commences at 8 pm day 1; then three times daily at 8am, 2pm, 8pm
- After 8am vaporization on day 5, plasma sampled for 12 hours for opioid and THC levels
- Subjects complete drug effects questionnaire re: pain and other symptoms during PK draws

Slide courtesy of D. Abrams
Pain Characteristics

- Musculoskeletal NOS 7
- Post-traumatic 4
- Arthritis 2
- Peripheral neuropathy 2
- Cancer 1
- Fibromyalgia 1
- Migraine 1
- Multiple sclerosis 1
- Sickle cell disease 1
- Thoracic outlet syndrome 1

Slide courtesy of D. Abrams
### Pain by Study Day

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Day 1 Mean (95% CI)</th>
<th>Day 5 Mean (95% CI)</th>
<th>Difference Mean (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>21</td>
<td>39.6 (35.8, 43.3)</td>
<td>29.1 (25.4, 32.8)</td>
<td>-10.7 (-14.4, -7.3) %Δ -27.2</td>
</tr>
<tr>
<td>Morphine</td>
<td>11</td>
<td>34.8 (29.4, 40.1)</td>
<td>24.1 (18.8, 29.4)</td>
<td>-11.2 (-16.5, -6.0) %Δ -33.7</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10</td>
<td>43.8 (38.6, 49.1)</td>
<td>33.6 (28.5, 38.6)</td>
<td>-10.3 (-14.8, -5.8) %Δ -21.3</td>
</tr>
</tbody>
</table>

* Bold indicates p<0.001

Slide courtesy of D. Abrams
Figure 1  Plasma concentration–time curves for sustained-release (a) morphine and (b) oxycodone before and after exposure to inhaled cannabis.
Conclusions

- Co-administration of vaporized cannabis with oral sustained release opioids is safe
- Co-administration of vaporized cannabis in subjects on stable doses of morphine or oxycodone appears to enhance analgesia
- 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
In studies...MARINOL Capsules has [sic] been co-administered with a variety of medications (e.g., cytotoxic agents, anti-infective agents, sedatives, or opioid analgesics) without resulting in any clinically significant drug/drug interactions ...cannabinoids may interact with other medications through both metabolic and pharmacodynamic mechanisms. Dronabinol is highly protein bound to plasma proteins, and therefore, might displace other protein bound drugs. Although ...not ...confirmed in vivo...
<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction with THC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>THC can increase the effect of fluoxetine.</td>
</tr>
<tr>
<td>TCAs</td>
<td>THC can increase the side effects of amitriptyline (i.e. tachycardia, hypertension and sedation).</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Indomethacin and acetylsalicylic acid (aspirin) reduce the effects of THC.</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>These increase the depressive effects of THC and also increase tachycardia associated with THC consumption.</td>
</tr>
<tr>
<td>BZDPS</td>
<td>These drugs can increase depression of the nervous system and also of the respiratory system.</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>These reduce tachycardia associated with THC.</td>
</tr>
<tr>
<td>ETOH</td>
<td>This can increase nervous system deterioration.</td>
</tr>
<tr>
<td>Opioids</td>
<td>Increased sedation and analgesia.</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Cannabinoids increase theophylline catabolism. A dosage increase is thus required in such cases.</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Atropine and scopolamine can increase tachycardia produced by THC.</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>THC interacts with disulfiram, causing a very unpleasant reaction in the patient. The combination of both substances should therefore be avoided.</td>
</tr>
</tbody>
</table>

Source: Author: Rafael Borràs, Member of the Col·legi de Farmacèutics de la Província de Barcelona. Information leaflet on cannabis for therapeutic purposes
CANNABINOID INTEGRATED PAIN MANAGEMENT

Best available evidence → it works and it reduces opioid-related harms
Even a little can go a long way: eg, 2010 chronic neuropathic pain Canadian study: “a single inhalation of 25 mg of 9.4% THC herbal cannabis TID for 5 days reduced the intensity of pain, improved sleep, and was well tolerated” (~2-3mg THC/inhalation)

Most patients in pain clinical trials have used 1:1 THC:CBD whole plant oral cannabis extracts → 2.7 mg THC+2.5 mg CBD/pump, max ~25mg each/day, in divided doses

Can be used concomitantly w/ LA opioid analgesics: eg, in patients taking LA opioid analgesics (mean: 62 mg BID morphine ER and 52 mg BID oxycodone ER) for various chronic pain conditions, addition of vaporized cannabis (0.9g, 3.56% THC) TID reduced reported pain by 27% (95% CI: 9-46%) in 5d study. No effect on opioid metabolites, aside from decrease in the max plasma conc of morphine sulfate; no effect on oxycodone kinetics
• General approach to cannabis initiation is ‘start low, go slow, and stay low’.
• For cannabis inhalation, start with 1 inhalation and wait 15 min*. Then, may increase by 1 inhalation every 15–30 min until desired symptom control achieved.
• Higher THC concentrations of herbal cannabis may allow utilization of lower amounts. Patients should titrate accordingly to avoid adverse events.
• THC-mediated side effects such as fatigue, tachycardia and dizziness are avoidable when starting dose is low and titration is slow.
• CBD can balance THC side effects, especially in daytime use, or when driving is required.
• Most patients use 1–3 g of herbal cannabis per day
• Most patients require 6–8 sprays of nabiximols per day for symptomatic relief
• Use of homemade oral oils or topicals may require much higher dried cannabis than utilised for inhalation.
• CBD-predominant preparations have fewer untoward psychotropic effects, and may require higher dosing.

MacCallum and Russo. Practical considerations in medical cannabis administration and dosing. European Journal of Internal Medicine, March 2018, Volume 49, Pages 12–19
CLINICAL PEARLS

• Titration (bedtime):
  Days 1–2: 2.5 mg THC-equivalent at bedtime. (may start at 1.25 mg if young, elderly, or other concerns).
  Days 3–4: if previous dose tolerated, increase by 1.25–2.5 mg THC at bedtime.
  Days 5–6: continue to increase by 1.25–2.5 mg THC at bedtime every 2 days until desired effect is obtained. In event of side effects, reduce to previous, best tolerated dose.

Titration (day and night):
  Days 1–2: 2.5 mg THC-equivalent once a day
  Days 3–4: 2.5 mg THC twice a day
  Increase as needed and as tolerated to 15 mg THC-equivalent divided BID-TID
  Doses exceeding 20–30 mg/day may increase adverse events or induce tolerance without improving efficacy.

• CBD-rich dosing: 5–20 mg per day of oral preparations divided BID-TID, which may reduce attendant expense.

MacCallum and Russo. Practical considerations in medical cannabis administration and dosing. European Journal of Internal Medicine, March 2018, Volume 49, Pages 12–19
THREE POTENTIAL ROLES FOR THE USE OF CANNABIS MEDICINES IN ONCOLOGIC PALLIATIVE CARE

Symptom palliation

Palliation of spiritual and existential suffering
  euphoria,
  aversive memory extinction,
  sensorium enhancement
  spiritual insight catalysis.

Facilitating right to access experimental treatment
  preclinical evidence and case-study reports with objective markers that suggest that cannabinoids might have disease-modifying effects, including anti-tumor activity
  Hope, safety, and monitoring

past 40 yrs, mainly in the 1970s and 1980s, 33 controlled trials including a total number of 1525 participants

In one study (n = 61), performed at the Bethesda Memorial Hospital in Boynton Beach, USA, it was demonstrated that THC was as effective as ondansetron in the treatment of delayed nausea and vomiting following chemotherapy

Absence of nausea was significantly greater in active treatment groups (THC group in 71%; ondansetron group in 64%) versus placebo (15%; p<0.05 vs. placebo for both groups). The combination of both drugs had no additional effects (improvement in 53% of patients). Noteworthy, nausea intensity and vomiting/retching were lowest in patients treated with THC.
THC EFFECTS ON TASTE & SMELL

- adult patients with advanced cancer and poor appetite and disturbed chemosensory perception
- Department of Agricultural, Food and Nutritional Science in the University of Alberta, Canada
- 46 patients were randomized and received either 2.5 mg THC twice daily or identical placebo capsules over a time period of 18 days
- Compared with placebo, THC-treated patients reported significantly improved ($p = 0.026$) and enhanced chemosensory perception ($p < 0.001$), and “tasted better” food ($p = 0.04$). Pre-meal appetite ($p = 0.05$) and proportion of calories consumed as protein ($p = 0.008$) increased significantly compared with placebo. Furthermore, THC-treated patients reported increased quality of sleep ($p = 0.025$) and relaxation ($p = 0.045$).

<table>
<thead>
<tr>
<th>Possible situation</th>
<th>Tips or suggestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient is naïve to medical cannabis. Which product should we recommend initially?</td>
<td>We suggest starting with a product that contains THC/CBD 1:1 ratio, as this will allow a better tolerance of possible THC side effects.</td>
</tr>
<tr>
<td>If using an oral product containing a THC:CBD ratio of 1:1, what is the maximum recommended initial dose in a naïve patient?</td>
<td>Since THC is the compound that will cause most of the unwanted side-effects, we suggest an initial dose of 2 mg THC + 2 mg CBD 1–2 hours before bedtime, and if tolerated slowly escalate the dose in increments of a maximum of 2 mg per day until therapeutic benefit or side effects are noted. Otherwise, a morning dose (BiD) or a 3 times per day (TID) schedule could be added if needed.</td>
</tr>
<tr>
<td>If using oral THC-rich or CBD-rich products, what is the maximum recommended initial dose of THC or CBD in a naïve patient?</td>
<td>In most cases, start with 2 mg of THC or 5 mg of CBD at 1–2 hours before bedtime, and if tolerated try to slowly escalate the dose, until therapeutic benefit or side effects are noted.</td>
</tr>
<tr>
<td>How should patients be initiated to an inhaled product?</td>
<td>Patients should start with a single inhalation, pausing briefly for 10–15 minutes between inhalations to ascertain either therapeutic and/or adverse effect.</td>
</tr>
<tr>
<td>Should patients hold their breath in order to maximize absorption when inhaling cannabis?</td>
<td>No. Inhaled cannabinoids are rapidly absorbed. Breath holding is not necessary and increases exposure to unwanted by-products. Patients should be advised to inhale fully but naturally and exhale in a relaxed way.</td>
</tr>
<tr>
<td>Patient reports fatigue, depression and/or insomnia with the CBD-rich product. What is the next step?</td>
<td>Try to reduce CBD dose, and consider a THC/CBD 1:1 product, or a THC-rich product (consider “sativa” varieties and terpenoids that could give stimulating effect such as Limonene and Pinene).</td>
</tr>
<tr>
<td>Patient is reporting palpitations, increased drowsiness and/or dizziness</td>
<td>Consider reducing THC dose since this is generally related to the possible cardiac and anxiogenic effects of THC.</td>
</tr>
<tr>
<td>Patient does not feel any effect (therapeutic or otherwise) one hour after taking his very first oral dose. Should he take another dose?</td>
<td>No! Peak effect with the oral route may take 3 hours or more. We suggest taking a single dose on the first few days of treatment and adjusting the dose only after 2 or 3 days. Even in the absence of therapeutic effects, this approach will allow to build tolerance for potential adverse effects, particularly in more frail patients.</td>
</tr>
<tr>
<td>Are there increased safety risks when patients use high-potency products?</td>
<td>Yes. A single inhalation of cannabis containing 25% THC could contain a dose capable of producing unwanted side-effects in a cannabis naïve patient. We recommend starting with a product containing a low to moderate THC content (10% or less).</td>
</tr>
</tbody>
</table>

THC, tetrahydrocannabinol; CBD, cannabidiol.
Research Article

The Medical Necessity for Medicinal Cannabis: Prospective, Observational Study Evaluating the Treatment in Cancer Patients on Supportive or Palliative Care

Gil Bar-Sela,1,2 Marina Vorobeichik,1 Saher Drawsheh,1 Anat Omer,1 Victoria Goldberg,1 and Ella Muller1

1 Division of Oncology, Integrated Oncology and Palliative Care Unit, Rambam Health Care Campus, 31096 Haifa, Israel
2 Faculty of Medicine, Technion-Israel Institute of Technology, 31096 Haifa, Israel
8 week study of 131 cancer patients who used cannabis under medical license

“All cancer or anti-cancer treatment-related symptoms, including nausea, vomiting, mood disorders, fatigue, weight loss, anorexia, constipation, sexual function, sleep disorders, itching, and pain had significant improvement,”

“The population of the prolonged users in the current study reported significant improvement in all aspects of supportive and palliative oncology care.”

Gil Bar-Sela, Integrated Oncology and Palliative Care Unit, Rambam Health Care Campus, Haifa. (as reported in NationalPainReport.com)
• 211 initially recruited; ~25% deceased before study end; 10% did not start treatment
• Nearly 1/3 patients who used medical marijuana reported significant relief from cancer related pain and discomfort.
• Of 70 patients who used opioid pain medications at start, 31 reduced the dose 8 wk later.
• 1/3 patients taking anti-depressant or anxiety drugs reported a reduction in dosage at end.
• 12% dropped out b/c they concerns of dizziness, fainting, nausea and psychosis they believed was caused by cannabis use, or lack of effect.
• There were no significant side effects reported, except for some memory loss (22% in 1st interview; 48% in 2nd)
RECENT ISRAELI STUDY ON CANNABIS USE IN NEARLY 3,000 CANCER PATIENTS

• N= 2970. Average age 59.5 ± 16.3 years, 54.6% women. Types of cancer: breast (20.7%), lung (13.6%), pancreatic (8.1%) and colorectal (7.9%) with 51.2% being at stage 4. Main symptoms requiring therapy: sleep problems (78.4%), pain (77.7%, median intensity 8/10), weakness (72.7%), nausea (64.6%) and lack of appetite (48.9%). After six months of follow up, 902 patients (24.9%) died and 682 (18.8%) stopped the treatment. Of the remaining, 1211 (60.6%) responded; 95.9% reported an improvement in their condition, 45 patients (3.7%) reported no change and four patients (0.3%) reported deterioration in their medical condition.

• showed a significant improvement in the control of other common symptoms, including sleep problems (70.8%), fatigue (55.9%), anxiety and depression (74.1%), and nausea and vomiting (54.7%).

• Only 18.7% of patients reported good quality of life prior to treatment initiation, while 69.5% reported good quality of life at 6 months.

• Furthermore, 36% of patients stopped using opioids and less than 20% discontinued their cannabis treatment. Of these, only 19.3% stopped due to side effects.

Characteristics of patients with chronic pain accessing treatment with medical cannabis in Washington State

Sunil K. Aggarwal, PhD, MD Candidate
Gregory T. Carter, MD, MS
Mark D. Sullivan, MD, PhD
Craig ZumBrunnen, PhD
Richard Mearl, PhD
Jonathan D. Mayer, PhD

ABSTRACT

Objectives: This study was conducted to better understand the characteristics of chronic pain patients seeking treatment with medical cannabis (MC).

Design: Retrospective chart review of 138 patients (87 males, median age 47 years, 52 females, median age 40 years), all were legally qualified for MC use in Washington State.

Setting: Regional pain clinic staffed by university faculty.

Participants: Inclusion criteria: age 18 years and older, having legally accessed MC treatment, with valid documentation in their medical records. All data were de-identified.

Main Outcome Measures: Records were scored for multiple indicators, including time since initial MC authorization, qualifying condition(s), McGill Pain score, functional status, use of other anaesthetic modalities, including opioids, and patterns of use over time.

Results: Of 138 patients, 115 (84.11 percent) had prior authorizations for MC before seeking care in this clinic. The sample contained 235.4 patient-years of authorized MC use. Time of authorized use ranged from 11 days to 51 years (median of 1.12 years). Most patients were males (63 percent) yet female patients averaged 0.16 years longer authorized use. There were no other gender-specific trends or factors. Most patients (n = 125, 91.1 percent) had more than one pain syndrome present. Myofascial pain syndrome was the most common diagnosis (n = 114, 82 percent), followed by neuropathic pain (n = 98, 64 percent), discogenic back pain (n = 72, 51.7 percent), and osteoarthritis (n = 57, 40.6 percent). Other diagnoses included diabetic neuropathy, central pain syndrome, phantom pain, spinal cord injury, fibromyalgia, rheumatoid arthritis, HIV neuropathy, visceral pain, and malignant pain. In 51 (37.7 percent) patients, there were documented instances of major barriers related to accessing MC, including prior physicians unwilling to authorize use, legal problems related to MC use, and difficulties in finding an affordable and consistent supply of MC.

Conclusions: Data indicate that males and females access MC at approximately the same rate, with similar median authorization times. Although the majority of patient records documented significant symptom alleviation with MC, major treatment access and delivery barriers remain.

Key words: cannabis, marijuana, cannabinoids, chronic pain, opioid, opiate

INTRODUCTION

Recently, there has been widening interest in the viability of the medicinal use of cannabis or marijuana, with a call for further research from the National Institutes of Health (NIH)² a statement of support for consideration of the reclassification of cannabis status as a Schedule I substance by the American College of Physicians (ACP), and a recommendation for clinical use of medical cannabis (MC) for symptom relief in seriously ill patients in limited and locally implemented peer-reviewed...
"In medicine there are two ways we deal with a patient story. If you don't like it, you call it an anecdote. If you like it, you call it a case history." - L. Dossey
### Table 1.1: Patient Sample Demographics. As of 5/31/08.

<table>
<thead>
<tr>
<th>Gender</th>
<th>n (%)</th>
<th>Mean Age ± SD (Yrs)</th>
<th>Median Age (Yrs)</th>
<th>Age Range (Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>87 (62.6)</td>
<td>46.6 ± 12.7</td>
<td>47</td>
<td>18-69</td>
</tr>
<tr>
<td>Female</td>
<td>52 (37.4)</td>
<td>46.2 ± 12.9</td>
<td>48</td>
<td>22-84</td>
</tr>
<tr>
<td>Total</td>
<td>139 (100)</td>
<td>46.4 ± 12.7</td>
<td>48</td>
<td>18-84</td>
</tr>
</tbody>
</table>

### Table 1.2: Clinic Catchment Area for Medical Cannabis Access. All 3-digit ZIP codes are in Washington state; *one patient had moved to Illinois.*

<table>
<thead>
<tr>
<th>3-digit ZIP code area of home address</th>
<th>Patient Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>985</td>
<td>100</td>
</tr>
<tr>
<td>983</td>
<td>14</td>
</tr>
<tr>
<td>986</td>
<td>9</td>
</tr>
<tr>
<td>981</td>
<td>7</td>
</tr>
<tr>
<td>984</td>
<td>2</td>
</tr>
<tr>
<td>980</td>
<td>2</td>
</tr>
<tr>
<td>991</td>
<td>2</td>
</tr>
<tr>
<td>982</td>
<td>1</td>
</tr>
<tr>
<td>993</td>
<td>1</td>
</tr>
<tr>
<td>605</td>
<td>1*</td>
</tr>
</tbody>
</table>

### Table 1.3: Patient-years of Authorized Medical Cannabis Use in Sample. As of 5/31/08.

<table>
<thead>
<tr>
<th></th>
<th>Patient-Years</th>
<th>Mean ± SD (Years)</th>
<th>Range</th>
<th>Carter-authorized Patient Years</th>
<th>Mean ± SD (Years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>145.3</td>
<td>1.67 ± 1.67</td>
<td>11 days - 8.31 years</td>
<td>135.1</td>
<td>1.55 ± 1.65</td>
<td>11 days - 8.31 years</td>
</tr>
<tr>
<td>Female</td>
<td>91.1</td>
<td>1.75 ± 1.64</td>
<td>50 days – 6.80 years</td>
<td>90.3</td>
<td>1.73 ± 1.64</td>
<td>50 days – 6.80 years</td>
</tr>
<tr>
<td>Total</td>
<td>236.4</td>
<td>1.70 ± 1.66</td>
<td>11 days - 8.31 years</td>
<td>225.4</td>
<td>1.62 ± 1.64</td>
<td>11 days - 8.31 years</td>
</tr>
</tbody>
</table>
Generated 138/0.06 = 2,300 dots, which were then spatially randomly distributed within each of their respective three-digit zip code boundary regions. One patient’s home zip code was in IL and is not shown here.
CHRONIC PAIN SYNDROMES IN MEDICAL CANNABIS PATIENT SAMPLE

Myofascial Pain Syndrome (MPS)
Diabetic Neuropathy (DN)
Neuropathic Pain Syndrome (NPS)
Central Pain Syndrome (CPS)
Phantom Pain (PP)
Spinal Cord Injury (SCI)
Fibromyalgia Syndrome (FMS)
Osteoarthritis (OA)
Rheumatoid Arthritis (RA)
Discogenic Back Pain (DP)
HIV Neuropathy (HIV)
Malignant Pain (MP)
Distribution of Chronic Pain Syndromes Diagnosed in Medical Cannabis-Using Patient Sample

>1 chronic pain syndrome in 88% of sample. No one >65 had just one chronic pain syndrome present.

MPS = Myofascial Pain Syndrome, DN = Diabetic Neuropathy
QUALITATIVE FEATURES OF PATIENT SAMPLE

Representative of a sub-specialty referral outpatient pain rehabilitation medicine clinic

14 with traumatic brain and closed head injuries, 9 with Hepatitis C virus, 4 with past history of gun shot wounds (one in the head), 3 with past history of shrapnel wounds, 5 with spinal cord injuries, 1 with ALS (amyotrophic lateral sclerosis), 1 with PLS (primary lateral sclerosis), 1 with myotonia congenita, 1 with HIV, and 19 with fibromyalgia

Patient Snapshots -- 9
- 52 yo M w/ chron. back, bilat. leg, bilat. shoulder pain 2/2 DJD, FSSS, mult. rotator cuff repairs
  (Patient #101; 985xx; MPS, NPS, OA, DP)
  - Medical cannabis authorization ~5 mo.
  - “He has been using marijuana on his own, as he feels [it] gives him the best pain relief of anything that he has used.” 2-3 inhalations on a MJ cigarette 2-3[x]/day, & this improves his pain levels drastically w/o incapacitating him.
  - Also using MS Contin
  - Barriers: “He is quite adamant noting that he has never been a recreational marijuana user and is adamantly against recreational drug use. He stated a number of times during our visit that he is embarrassed to inquire about this.”

- 18 yo M w/ chron. head and neck pain 2/2 TBI (bike vs. motor home, GCS 4)
  (Patient #7; 985xx; MPS, CPS)
  - Medical cannabis authorization 4 mo.
  - “using MJ successfully on a daily basis; pain from 8-9/10—>2-3/10; needs only ~2-3 inhalations from a MJ cigarette to get pain relief”
  - “Has difficulty tolerating opioid medications”
  - Barriers: May 22, 2008: Department of Corrections (DOC) process was disallowing his MMJ use
• 35 yo F w/ severe L ulnar neuropathy since 1996, s/p surg., OA-rel. LBP & hip pain  
  *(Patient #38; 985xx; MPS, NPS, OA)*  
  • medical cannabis authorization >2.5yrs  
  • “marijuana daily with no SE; only thing she is now currently using for pain”;  
  • oxy/APAP rarely,

• 39 yo F w/ chron. daily migraine HA’s w/ myofascial component, SA cyst in L T lobe, mult. MSK probs.  
  *(Patient #67; 980xx; MPS, CPS, OA)*  
  • medical cannabis authorization >7mo  
  • “She has been using cannabis in the past and has had excellent results with respect to her migraine headaches.” Using <1/4 oz/week  
  • also uses gabapentin

• 65 yo M w/ ALS (diag'd in 2004) -- terminally ill -- increasing weakness, pain, dysphagia, dysarthria. S/p gastrostomy.  
  *(Patient #58; 986xx; NPS)*  
  • medical cannabis authorization 3.38yrs  
  • uses amitryptaline
• 50 yo M w/ chron. abd pain 2/2 chron. active HCV; chron. neck & back pain 2/2 C- & L- DJD+DDD; s/p splenectomy for mass; Hx of panic d/o (Patient #126; 985xx; MPS, DP, VP)
  
  • Medical cannabis authorization ~13 months
  • “states openly that he has used marijuana in the past and it has helped his pain substantially. Tolerates it much better than opiates and his use of marijuana has substantially decreased his dependence on opiates”
  • Previously was taking Oxycontin 40-80mg BID; since using MMJ, now completely off oxy and only using hydrocodone/APAP prn

• 53 yo M w/ chronic C myelopathy 2/2 to stenosis w/ Hx of ACDF; chronic neuropathic pain (radicular sx’s); Hx of chron. rotator cuff impairment on L, status-post surg., L- DJD+DDD, erosive OA, Sjoren’s (Patient #133, 985xx; MPS, NPS, OA, DP)
  
  • Medical cannabis authorization 14 mo
  • “he is using MC to control his pain with good luck with that. He also uses oxycodone and oxyContin, but he tries to limit this.” (5/20/08); “Cannabis daily for pain control” (4/10/07)
  • Reported Oxycodone/Contin SE’s of constipation/nausea; also used celebrex and cortisone injections
  • Barriers: Told by another MD on October 26, 2006: “He does need to quit using marijuana for safe general anesthesia.”
• 22 yo M w/ chronic back pain 2/2 to Hx of spinal compression Fx's T10-T12, s/p fusion. Trauma on 2/23/03: snowboarding acc. @ Whitepass; went off a jump, came down on R shoulder-immed., excruciating, pain)

(Patient #24; 985xx; MPS, DP)

• Medical cannabis authorization ~1.8 yrs
• “poor tolerance to opioids...finds too sedating; also uses cymbalta, IBP; tramadol and flexaril--he didn’t think they helped much; has received trigger pt injections”
• Barriers: Partner doctor in practice would not authorize

• 33 yo F w/ HIV-related peripheral neuropathy, on dual ARV Tx (HIV+ Dx on 3/9/99; exposure to unprotected sex); Hx of FMS and MDD

(Patient #22, 985xx; FMS, HIV)

• Medical cannabis authorization 2.13 yrs
• uses 2oz of cannabis/month; approx. 2g smoked/day to relieve pain, although sometimes more; cannabis use tx's pain 7-8-->2-3
• does not tolerate narcotics, which make her nauseated and worsen appetite; allergic to morphine+demerol; uses loperimide for nausea
• Barriers: involved in some type of legal alteration where she was arrested for possession of marijuana. Was authorized by a previous MD who moved. "She was a good candidate for MMJ at time of arrest."
OBSERVATIONS AND INFERENCES

- Major hurdles rel. to MC access in 37%, e.g., prior physicians unwilling to authorize, legal problems related to use, and difficulties finding affordable and consistent supply.

- Specific data indicating MC better than all other pain medications used in past and, in some cases, only medication found effective -- 26 patients (19%).

- Methodology → difficult to make definitive statements regarding opioid/MC use rel.

- No documentation of cessation of MC use for any reason (intolerance, e.g.).

- Helps deconstruct myths about kinds of patients accessing MC treatment: 1) not young males; 2) not malingers; 3) not feigning disease to access cannabis.

- Subjective and objective diagnostic data shows MC patients are middle aged women and men, with complex medical problems.

- Such results from tertiary care pain rehab clinic directed by a qualified physician in academic medicine should help to dispel stereotypes about valid and invalid treatment with botanical and non-botanical cannabinoid-based medicines (a la Dr. Pot and Dr. Pat).
THANK YOU!

- www.cannabinologist.org

- Washington State Healthcare Provider Continuing Education: Medical Use of Marijuana course - now available for registration!

- The "Washington State Healthcare Provider Continuing Education: Medical Use of Marijuana" online course has been adopted, accredited by the State of Washington and is now available for participant registration. Learn more about the course on our website.