Medical Use of Cannabinoids in Palliative Care

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- Multiple Sclerosis (Canada)
  http://www.youtube.com/watch?v=88_5EbsjK8I
- Seizures (Colorado)
  http://www.tokeofthetown.com/2013/02/powerful_video_shows_ins	ant Relief_for_epileptic_cannabis_patient.php
- CP Stutter (Missouri)
  http://sploid.gizmodo.com/watch-%e2%80%93_the-%e2%80%93instant-%e2%80%93change-%e2%80%93when-girl-with-
cerebral-palsy-1478892426
- Parkinson’s (Israel)
  http://www.youtube.com/watch?v=rHmbNjCNRQM
- Severe Tourette’s (Germany)
  http://www.youtube.com/watch?v=plnkduXOQac

Disclosure
No relevant financial conflicts related to this subject.

Objectives
1. Describe the pharmacology of cannabinoids
2. Name 3 indications for the use of cannabinoids in palliative care
3. Recognize the side effects and potential harms of medical marijuana use
Outline

- Background of cannabinoids
  - History
  - Pharmacology
- Medical Use in Palliative Care
  - Cannabis
  - Synthetic cannabinoids
- Side Effects and Safety Concerns
- Legal and Ethical Issues

Background

A SHORT HISTORY OF CANNABINOIDS

Notable history of cannabis

- **Shen Nung**, an emperor of China (also the discoverer of tea and ephedrine), is held to be among the first to report on therapeutic uses of cannabis in a medicinal compendium that dates to 2737 BCE.

- In 1839, William O’Shaughnessy, a British doctor working in India, published a paper on cannabis as an analgesic and appetite stimulant that also tempered nausea, relaxed muscles, and might ameliorate epileptic seizures.
  - Led to widespread medical use of cannabis in the United Kingdom (e.g. it was prescribed to Queen Victoria for relief of menstrual discomfort)

Legal prohibition of cannabis for medical use in the U.S.

- **1937:** Harry J. Anslinger, a prominent prohibitionist, successfully lobbied Congress to pass the Marihuana Tax Act, making access to the plant costly.
  - Anslinger was the head of the Federal Bureau of Narcotics and presented cannabis use to the public as an unalloyed danger, resulting in “reefer madness.”
  - The AMA opposed the Marihuana Tax Act, fearing that it would limit medicinal study and potential prescription of the plant.
- **1942:** Marijuana was removed from the United States Pharmacopeia, a compendium that set standards for medicines and foods.
- **1970:** Congress enacted the Controlled Substances Act, classifying marijuana along with heroin as a Schedule I drug.


Overview of Cannabinoid Pharmacology

- Cannabis strains may vary by morphology, odor, and chemotype, producing plant resin with varying ratios of pharmacologically active cannabinoids, principally **tetrahydrocannabinol (THC)** and **cannabidiol (CBD)**, terpenoids, flavonoids, and other molecules.

- Although other receptors play a role, the majority of the effects of THC from cannabis are mediated through partial agonism of central and peripheral cannabinoid receptors, **CB1** and **CB2**, respectively.

- Activation of CB1 and CB2 directly inhibits the release of multiple neurotransmitters including **acetylcholine**, **dopamine**, and **glutamate** while indirectly affecting **γ-aminobutyric acid**, **N-methyl-D-aspartate**, **opioid**, and **serotonin** receptors.

Russo EB. *Br J Pharmacol*. 2011;160:1344-64.
Overview of Cannabinoid Pharmacology

• Cannabinoid receptors (CB1, CB2) are part of the endocannabinoid system (ECS), a pro-homeostatic modulatory system composed of several endogenous ligands (e.g. anandamide and 2-arachidonylglycerol)

• Physiologically, the ECS been shown to impact pain perception, movement, appetite, aversive memory extinction, hypothalamic-pituitary-adrenal (stress) axis modulation, immune function, mood, inflammation, and others.

Russo EB. Br J Pharmacol. 2011; 163:1344-64.

CB1 Receptor Activation

Cannabinoid binding (activation)

- negatively coupled to adenylate cyclase,
- suppresses neuronal Ca^{2+} conductance,
- inhibits inward rectifying K^+ conductance

- suppression of neuronal excitability

Cannabinoid receptors are found in the pain neural matrix

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
Regulation of nausea and vomiting by the endocannabinoid system

- CB1 receptors are found in the dorsal vagal complex (medullary nucleus solitarius, area postrema, dorsal motor nucleus of the vagus).
- CB1 receptor agonists reduce in intestinal 5-HT release, suggesting enterochromaffin cells express functional CB1 receptors.
- Cannabinoid inhibition of 5-HT3 receptor activity in this region—increased GABAergic activity
- Receptor-independent pathways too


Anti cancer properties?

1. Cannabinoids induce cancer cell death
2. Cannabinoids inhibit angiogenesis, invasion and metastasis


Pharmacokinetics

- 95-99% THC is plasma protein bound (lipoproteins)
- Metabolism via hydroxylation, oxidation, and conjugation (CYP2C9 and CYP3A)
  - First-pass metabolism with oral admin. (11-OH-THC)
- Rapidly cleared from plasma (70% tissues / 30% metabolized)
- Elimination over several days (adipose)
- THC is excreted via both hepatic and renal mechanisms.
  - No specific studies have been done with cannabis-based medicines in patients with significant hepatic or renal impairment, but it can be expected that effects would be more exaggerated or prolonged in these settings.
- 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]

MEDICAL CANNABIS

SYMPTOM MANAGEMENT IN PALLIATIVE CARE
The evidence

- Over the last several decades cannabis and cannabinoid therapeutics have been studied in over 100 controlled clinical trials of varying size and quality, investigating a wide range of conditions.

- As with the evidence for most pharmacologic symptom interventions, there are a lack of comparative data between cannabis and other commonly used treatments.

Hill KP et al. JAMA 2015;313(24):2474–2483

- Total: 24,023 – 2.3 publications/day for last 20 years
- 2013 projected: 280 in first 38 days

Slide courtesy of Sunil Aggarwal, MD

Cancer Pain

- For cancer pain, a multicenter RCT, involving 360 patients, investigated oral cannabis to treat breakthrough cancer pain in subjects who were started on a long-acting opioid.
- It showed analgesic efficacy in the low and medium dose ranges, which were also well-tolerated.


Painful Neuropathy

- Two RCTs of inhaled cannabis for painful HIV sensory neuropathy involving 89 subjects in total showed significant analgesic efficacy, with a combined NNT of 3.38, superior to all other medications similarly tested for this indication.

Chronic, intractable neuropathic pain

- Three RCTs of inhaled cannabis for chronic, intractable neuropathic pain due to multiple etiologies, involving 100 subjects in total, all showed efficacy for smoked and vaporized cannabis.


Nausea and Vomiting

- Three RCTs, involving 43 subjects in total, investigating inhaled cannabis for nausea and vomiting secondary to active cancer chemotherapy, demonstrated inhaled cannabis to be an efficacious antiemetic.


Appetite Stimulation for Anorexia

- Three RCTs of inhaled cannabis involving 107 subjects in total congruently showed efficacy for appetite stimulation and weight gain in patients with AIDS wasting syndromes.
- No studies have reported a benefit in cancer patients.


Spasticity in Multiple Sclerosis

Spasticity (both objective and subjectively assessed), spasm frequency, insomnia, pain, and impaired mobility—were shown to be significantly improved in a 630 subject multicenter RCT over a 12-month period.

Prescribing medical marijuana

- Exact dosages depend on individual patient need and tolerance of side effects. No evidence based guidelines on dosing have been developed.
- Cannabis preparations include:
  - resin-containing herbal flowers, which can be heated and delivered to the lungs via inhalation of smoke or vapor,
  - cannabis-based extracts, which include oral, oromucosal, rectal, and topically delivered preparations in the form of concentrates, suppositories, edibles, and salves.

Aggarwal S, Blinderman CD. Fast Facts #279 JPM, 2014
Nausea and Vomiting

- Dronabinol and nabilone are FDA approved for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond to conventional antiemetics.

- There are no published studies comparing dronabinol and nabilone to newer antiemetic agents.

Arnold RM, Wilner LS. Fast Facts #93 Cannabinoids In The Treatment Of Symptoms In Cancer And AIDS

Orexigenic (appetite stimulation)

- Only dronabinol is FDA approved for the treatment of anorexia associated with weight loss in patients with HIV/AIDS.
  - Early studies of dronabinol in this population showed promising increases in caloric intake and stabilization or gains in weight.
  - However, later analysis showed that the effect sometimes represented accumulation of water or fat instead of the preferred lean body mass.

- Neither dronabinol or nabilone are indicated for cancer associated anorexia.

Arnold RM, Wilner LS. Fast Facts #93 Cannabinoids In The Treatment Of Symptoms In Cancer And AIDS

Dosing synthetic cannabinoids

- Dronabinol (Marinol)
  - Chemotherapy induced N/V: 5mg/m² PO 1-3 hours before and Q2-4 hr after chemo; may be increased in 2.5mg/m² increments to 15mg/m²; not to exceed 4-6 doses/day
  - Appetite stimulation: 2.5mg PO Q12hr, may be increased to 20mg/day

- Nabilone (Cesamet)
  - Chemotherapy induced N/V: 1-2mg PO Q8-12h
Safety and Public Health Concerns

Safety:
- Occasional and low cumulative marijuana use was not associated with adverse effects on pulmonary function (Pletcher MJ, et al. JAMA 2012)
- Medical cannabis laws (from 1999-2010) are associated with significantly lower opioid overdose mortality rates. (Bachhuber MA, et al. 2014)
- Unlike opioid overdose, marijuana toxicity is not fatal.

Concerns:
- Marijuana adverse effects—acute and chronic (Volkow ND, et al. NEJM, 2014)
- Increased risk of MVA’s with acute marijuana impairment (Hartman RL, Huestis MA. Clin Chem, 2013)
- Preliminary research points to an association between marijuana use and MI, stroke, and PVD (Thomas G, et al.. Am J Cardiol. 2014)

Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.

Effects of short-term use
- Impaired short term memory
- Impaired motor coordination, interfering with driving skills and risk of injuries
- Altered judgment, increasing risk of sexual behaviors, transmission of STDs
- High doses: paranoia and psychosis

Effects of long-term or heavy use
- Addiction
  - ~9% of users overall, 17% of those who begin use in adolescence, and 25-50% of daily users
- Altered brain development
- Poor educational outcome, increased likelihood of dropping out of school
- Cognitive impairment
- Diminished life satisfaction and achievement
- Symptoms of chronic bronchitis
- Increased risk of chronic psychosis disorders in persons with predisposition

Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Overall Level of Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction</td>
<td>High</td>
</tr>
<tr>
<td>Abnormal brain development</td>
<td>Medium</td>
</tr>
<tr>
<td>Progressions to use of other drugs</td>
<td>Medium</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Medium</td>
</tr>
<tr>
<td>Depression or anxiety</td>
<td>Medium</td>
</tr>
<tr>
<td>Diminished motor achievement</td>
<td>High</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>High</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
<td>High</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Low</td>
</tr>
</tbody>
</table>

*The indicated overall level of confidence is the association between marijuana use and the listed effects represents an attempt to rank the strength of the current evidence, especially with regard to heavy or long term use and use that starts in adolescence.
Increases over Time in the Potency of Tetrahydrocannabinol (THC) in Marijuana and the Number of Emergency Department Visits Involving Marijuana, Cocaine, or Heroin.

Synthetic Cannabinoids: “Legal Alternative to Marijuana”

Past-Year Use of Illicit Drugs by High School Seniors (percent)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana/Hashish</td>
<td>36.4</td>
</tr>
<tr>
<td>Synthetic Marijuana</td>
<td>11.3</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>4.8</td>
</tr>
<tr>
<td>Salvia</td>
<td>4.4</td>
</tr>
<tr>
<td>MDMA (Ectasy)</td>
<td>3.8</td>
</tr>
<tr>
<td>Cocaine</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Source: University of Michigan, 2015 Monitoring the Future Study

Clusters of Cases of Adverse Health Effects or Severe Toxic Effects and Deaths Associated with Synthetic Cannabinoid (SC) Product Use.

LEGAL AND ETHICAL ISSUES

Integrating medical marijuana in clinical practice

Legal and Ethical Issues

• Federal law vs state law
  — Annas, G. NEJM, 2014

• Protection to discuss marijuana as part of doctor-patient confidentiality
  — Protected under federal law even in states where it is illegal to prescribe

• Conflict of interest
  — Should physicians who serve as “scientific advisors” to marijuana growers/suppliers be allowed to prescribe?

Take Home Points

• Cannabinoids act on unique G-protein receptors (CB1 and CB2) found in the CNS, immune system, and elsewhere in the body.

• High quality studies have demonstrated that cannabinoids can be of benefit in patients with cancer pain, neuropathic pain, anorexia, nausea/vomiting, and spasticity.

• There are no evidence-based dosing guidelines for inhaled or ingested cannabis.

• Side effects (short and long term) may be significant and should be reviewed with patients in whom cannabinoids are being considered.

Questions?