Treating the Whole Person: Optimizing Wellness
Friday, December 8, 2017
Greenwich, CT

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Vireo Health

Assistant Clinical Professor
| Family Medicine & Community Health |
| ICAHN |
Many Names
Stigma

“IF CANNABIS were unknown, and bioprospectors were suddenly to find it in some remote mountain crevice, its discovery would no doubt be hailed as a medical breakthrough. Scientists would praise its potential for treating everything from pain to cancer, and marvel at its rich pharmacopoeia—many of whose chemicals mimic vital molecules in the human body.”

The Economist April 27, 2006
http://www.economist.com/node/6849915
General and Historical Background

- The cannabis plant (Cannabis sativa, C. indica and C. ruderalis) is an annual flowering herb
- It has more than 60 unique compounds (>500 total)
- Δ-9-tetrahydrocannabinol (THC) is intoxicating
- Cannabidiol (CBD) is not; may ameliorate some THC effects
- Earliest recorded use of medicinal cannabis (“ma”) dates back to 2900BC - Emperor Fu Hsi
- Emperor Shen Nung discovers healing property (2700BC)
Cannabis Plant SPREAD
General and Historical Background

- The cannabis plant (*Cannabis sativa, C. indica and C. ruderalis*) is an annual flowering herb.
- It has more than 60 unique compounds (~480 total).
- $\Delta-9$-tetrahydrocannabinol (THC) is psychoactive.
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Marinol® (Dronabinol, THC) Review*
**Marinol® (Dronabinol, THC) Review**

- **Dose:**
  - CINV: 5mg/m² PO 1-3h prior to chemo, then every 2-4h after.
  - AIDS/cancer anorexia: 2.5mg PO before lunch and dinner

- **Contraindications, Warnings and Precautions:**
  - CI: allergy to sesame oil
  - History of addiction or drug abuse, mental illness

- **Adverse Drug Reactions:**
  - Psychoactive effects (24% for CINV), dizziness/drowsiness, hallucinations, anxiety, altered mental state

- **Major DDI’s:**
  - Ethanol (↑absorption, ↑ADR’s), amphetamines (↑BP, ↑HR)
ENTOURAGE
Natural Antagonism

THC
- euphoria
- anxiety
- psychosis
- cognitive impairment
- tachycardia

CBD
- no (or less) euphoria
- anti-anxiety
- anti-psychotic
- neuroprotective
- bradycardia

Loss of antagonism may lead to increased side effects and poor tolerability.

(Russo. Br J Pharmacol. 2011)
**Biological Components of Cannabis**

**Cannabinoids**
- THC*
- CBD*

**Minor Cannabinoids**
- CBC, CBG*, CBN*, THC-V*, CBD-V*, THCA*, CBDA*, CBC-V,

**Terpenes**
- trans-caryophyllene#, α-caryophyllene#, α-pinene, β-pinene, terpinolene, myrcene, limonene, Linalool, phytol, squalene

**Carotenoids**
- β-carotene#

**Fatty Acids**
- Linoleic acid, Palmitoleic acid, Linolenic acid, Palmitic acid, Oleic acid, Stearic acid, Myristic acid, Arachidonic

**Sterols**
- β-sitosterol, campesterol, stigmasterol

**Vitamins**
- Vitamin E

**Triglycerides**
ECS (ENDOCANNABINOID SYSTEM)
ENDOCANNABINOIDS

- Thermoregulatory centers
- Regulation of perceptive, cognitive, motor functions
- Suggested roles in synaptic plasticity, brain development
- Hypothalamic hormone secretion
- Release of dynorphins-analgesic
- Blood pressure and heart rate
ENDOCAANABINOIDS and pain

Pain hypersensitivity mechanisms at a glance

Vijayan Gangadharan and Rohini Kuner
ENDOCANNABINOIDS and pain

- Endogenous neuromodulators
- Similar location to opioid receptors:
  - Peripheral nociceptive nerves
  - Sensory neuron transduction pathway
  - Descending modulatory pathways
- One key difference
  - Absence in the brainstem

(Roquem, Nature Reviews, 2012)
Endocannabinoid Imbalance

- Migraine
- Fibromyalgia
- Causalgia
- Post-traumatic stress disorder (PTSD)
- Bipolar disease
- Autism
- Epilepsy
- Neurodegenerative disease

(Russo, Cannabis and Cannabinoid Research. 2016)
Prevalence of Use and Legal Status

- **28 States** (plus the District of Columbia and Guam) have legislature in place for medicinal cannabis.
- Some States have legalized it recently, but have no programs implemented yet (MD, NH, PA).
- Estimates of over 2,600,000* medicinal cannabis patients in the USA.
- *Some States have voluntary registration (CA, ME) or do not have any registration policies (WA).
- 11 States (AL, FL, IA, KY, MS, MO, NC, SC, TN, UT, WI) have passed laws legalizing some aspect.*
Prescribing or Recommending?

- Prescribers can’t prescribe medicinal cannabis on an Official New York State Prescription Blank, but they can “recommend” it on separate forms.

- On the recommendation form must be written:
  - **Patient-specific information** (like a regular prescription)
  - Authorized cannabis **brand** and **formulation**
  - **Dosing** information for patient’s proper use
  - Any **limitations** to the use of the approved product
  - The **total amount** of product that can be dispensed

- Quantity can NEVER exceed a 30 day supply!

- Prescriber must retain records for 5 years.
QUALIFYING CONDITIONS

Prescribers must be qualified to treat ≥1 of the following chronic health conditions:

1. Cancer
2. HIV/AIDS
3. Epilepsy
4. Neuropathies
5. Amyotrophic lateral sclerosis (ALS)
6. Huntington’s disease
7. Parkinson’s disease
8. Multiple sclerosis (MS)
9. Inflammatory bowel disease (IBD)
10. Damage to spinal cord nervous tissue with intractable spasticity
11. Chronic Pain (Recently Added)

The Commissioner may add or remove approved conditions.
Disease-Accompanying Symptoms

- One or more of the conditions **must** include:
  1. Severe or chronic pain causing a substantial limitation of function
  2. Severe nausea
  3. Seizures
  4. Cachexia or wasting syndrome
  5. Severe or persistent muscle spasms
     - The Commissioner may add or remove disease-accompanying symptoms
What is Different about NY?

- Licensed Pharmacists/Medical Model
- CO2 Extraction
- Formulation/”Real Dose”
- Physician/Provider recommendation
- Precision of final product
- 3rd Party testing (Heavy metals, bacteria, etc)
- Only active ingredients matter (major cannabinoids)
- No popularized names/strains
- No advertising
- 11 Qualifying Conditions
Overall Process

Cultivation
- Cloning
- Vegetative Growth
- Flowering
- Harvest
- Drying
- Grinding

Extraction
- Decarboxylation
- Extraction
- Winterization

Formulation
- Mixing with Excipient
- Quantitation of Cannabinoid Content
- Adjustment
- Quality Assurance

Packaging
- Primary Packaging
- Secondary Packaging
- Labeling

Distribution
- Transport to Dispensary
- Dispensing to Patients
STRAINS
Approved Products

- **THC Dominant**
  - **Red**: THC Dominant Cannabis Product
- **Balanced THC-CBD**
  - **Yellow**: THC Dominant Cannabis Product
  - **Green**: THC/CBD (1:1) Cannabis Product
- **CBD Dominant**
  - **Blue**: CBD Dominant Cannabis Product
  - **Indigo**: CBD Dominant Cannabis Product

THC Level

CBD Level

vireo NEW YORK
Delivery Forms

- **CAPSULES**
  - Green Capsules, 30 Capsules: $86.00

- **VAPORIZERS**
  - Green Prefilled Vaporizer Cartridge, 0.5mL Cartridge: $94.00

- **ORAL SOLUTION**
  - Green Oral Solution, 12.5mL Bottle: $165.00
<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Capsules</td>
<td>1 to 3 hr</td>
<td>4 to 24 hr</td>
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<tr>
<td>Oral solutions</td>
<td>30 to 60 min</td>
<td>4 to 12 hr</td>
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<tr>
<td>Tinctures</td>
<td>15 to 60 min</td>
<td>2 to 8 hr</td>
</tr>
<tr>
<td>Vapes and Oil</td>
<td>1 to 15 min</td>
<td>2 to 6 hr</td>
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**STRENGTH OF evidence vs. Harm grading**

<table>
<thead>
<tr>
<th>Rating Options</th>
<th>Arrow</th>
<th>Icon</th>
<th>Example</th>
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</thead>
<tbody>
<tr>
<td>(A,1)</td>
<td>↑</td>
<td>A↑</td>
<td>Exercise in DM</td>
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<tr>
<td>(A,2) (B,1)</td>
<td>↑</td>
<td>A₂ B₁</td>
<td>Hypnosis for IBS</td>
</tr>
<tr>
<td>(A,3) (B,2) (C,1)</td>
<td>→</td>
<td>A₃ B₂ C₁</td>
<td>Zinc in Infectious Diarrhea</td>
</tr>
<tr>
<td>(B,3) (C,2)</td>
<td>→</td>
<td>B₂ C₂</td>
<td>Opioids in Chronic Pain</td>
</tr>
<tr>
<td>(C,3)</td>
<td>↓</td>
<td>C₃</td>
<td></td>
</tr>
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Strengths of evidence vs. harm grading:
- Gives more credibility to therapies that have little potential harm. e.g. social support, reducing stress, and enhancing spiritual connection
- Helps us honor our primary goal, which is to “first, do no harm.”
# Levels of Evidence

<table>
<thead>
<tr>
<th>Grade A</th>
<th>Based on consistent, good-quality, patient-oriented evidence (e.g., systematic review or meta-analysis showing benefit, Cochrane Review with clear recommendation, high-quality patient-oriented randomized controlled trial). Example: Acupuncture for nausea and vomiting.</th>
</tr>
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<tr>
<td>Grade B</td>
<td>Based on inconsistent or limited-quality patient-oriented evidence. Example: Ginger for osteoarthritis.</td>
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<tr>
<td>Grade C</td>
<td>Based on consensus, usual practice, opinion, disease-oriented evidence (e.g., study showing a reduction in blood sugar but no studies in humans to show a benefit to those with diabetes).</td>
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## GRADING POTENTIAL HARM

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<thead>
<tr>
<th>Grade 3</th>
<th>This therapy has the potential to result in death or permanent disability. Example: Major surgery under general anesthesia or carcinogenic effects of the botanical Aristolochia (birthwort).</th>
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<td>Grade 2</td>
<td>Grade 2 (moderate harm) This therapy has the potential to cause reversible side effects or interact in a negative way with other therapies. Example: Pharmaceutical or nutraceutical side effects.</td>
</tr>
<tr>
<td>Grade 1</td>
<td>This therapy poses little, if any, risk of harm. Examples: Eating more vegetables, increasing exercise, elimination diets, encouraging social connection.</td>
</tr>
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</table>
We’re caught in the middle - InCrowd survey

- InCrowd survey of 225 U.S. primary care, emergency department, and pain medicine physicians
  - 73% survey respondents said they want opioid alternatives (tired to trying to treat pain with NSAIDs, PT and exercise)
  - 50% recommended behavioral health interventions
  - 20% recommended vitamin and herbal supplements
  - 10% recommended medical cannabis (InCrowd, 2016)
Detailed list of more than 150 peer-reviewed studies

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Title</th>
<th>Authors</th>
<th>Journal</th>
<th>Year</th>
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<td>151</td>
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**Note:** The table above includes only a subset of the detailed list of peer-reviewed studies. For a complete list, refer to the original source material.
AT LEAST five high-quality randomized controlled clinical trials establishing the pain relieving efficacy of cannabis

Synergy with opioids

Individuals with chronic pain requiring opioids (musculoskeletal, post-traumatic, arthritic, peripheral neuropathy, cancer, fibromyalgia, migraine, MS, sickle cell disease, TOS).

Synergistic effects with opioids, providing pain relief with lower opioid doses and with less side effects. Did not change opioid blood levels.

(Abrams, 2011)
GW pharmaceuticals phase 3 trials of nabiximols (Sativex) show benefit for cancer pain

- Randomized 360 subjects to placebo or one of three experimental groups
- Best results with 4 sprays per day (10mg THC / 10 mg CBD)
- Higher doses were not well-tolerated
  - more adverse events
  - higher dropout rates.

![Graph showing adjusted mean change from baseline in NRS average pain score](Portenoy 2012)
Patients with chronic pain successfully substitute medical cannabis for opioids

- Online survey of 244 medical cannabis patients with chronic pain to examine whether medical cannabis changed individual patterns of opioid use
- N=184 analyzed
- Found that cannabis was associated with
  - Decrease in opioid use (64%)
  - Improved quality of life (45%)

<table>
<thead>
<tr>
<th>Medication type</th>
<th>Use before initiation of cannabis (n/N)</th>
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</tr>
</thead>
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<tr>
<td>Opioids</td>
<td>119/184 (65%)</td>
<td>33/184 (18%)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>115/184 (62%)</td>
<td>38/184 (21%)</td>
</tr>
<tr>
<td>Disease-modifying antirheumatic drugs (DMARDs)</td>
<td>15/184 (8%)</td>
<td>3/184 (2%)</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>72/184 (39%)</td>
<td>25/184 (14%)</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitors (SNRIs)</td>
<td>15/184 (7%)</td>
<td>3/184 (2%)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
<td>34/184 (18%)</td>
<td>8/184 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>69/184 (38%)</td>
<td>40/184 (22%)</td>
</tr>
</tbody>
</table>

NOTE. Study participants reported using fewer medication classes of all categories after initiation of cannabis.

(Boehnke, Journal of Pain, 2016)
Cannabis is a beneficial adjuvant on all steps of analgesic ladder

- Synergistic actions between cannabinoids and opioids can lower dose of opioids needed to control pain
- Cannabis-based medicine containing both THC and CBD appears to be more effective and better tolerated than synthetic THC (dronabinol)
- Modified WHO analgesic ladder includes cannabinoids as adjuvant medications that may be considered at all steps of treatment of cancer or other chronic pain [1]

(Vargas-Schaffer, Can Fam Phys, 2010)
NNT - Painful sensory neuropathy

(Number Needed to Treat)

<table>
<thead>
<tr>
<th>Medication</th>
<th>NNT</th>
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<tbody>
<tr>
<td>Tricyclics</td>
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<tr>
<td>Cannabis</td>
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<td>Gabapentin</td>
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<tr>
<td>Lamotrigine</td>
<td>5.4</td>
</tr>
<tr>
<td>SSRIs</td>
<td>6.7</td>
</tr>
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</table>

*(AMA Ethics Virtual Mentor. May 2013)*
Efficacy Data: MINNESOTA DEPARTMENT OF HEALTH - ONE YEAR

![Bar chart showing reported benefit levels]

- No to little (1-2): 10% Patients (n=238), 24% Providers (n=142)
- Mild to moderate (3-5): 24% Patients, 31% Providers
- Significant (6-7): 66% Patients, 46% Providers
MEDICAL CANNABIS CONTRAINDICATIONS

- **Absolute contraindications**
  - Acute psychosis and other unstable psychiatric conditions

- **Relative contraindications**
  - Severe cardiovascular, immunological, liver, or kidney disease, especially in acute illness
  - Cannabis may exacerbate arrhythmia or a history of arrhythmias

(Handbook on Cannabis 2015)
MEDICAL CANNABIS CAUTIONS

- Cannabis is generally well-tolerated, and serious adverse effects, including increased risk of cardiovascular events, are rare.
- Adverse changes in cognitive function, especially executive function, may occur, especially with fetal or adolescent exposure.
- Cannabis should be avoided by adolescents, pregnant women, and nursing mothers.
- Cannabis should be avoided in those at risk of psychosis.
- Many studies show driving impairment, but on a much lower scale than alcohol.
- Drug interactions are a concern.
  - Cannabis enhances CNS depressant effects when combined with alcohol, barbiturates and benzodiazepines, but probably not opioids
  - THC induces CYP1A2, and can reduce levels of drugs metabolized by CYP1A2.
  - CBD inhibits CYP3A4 and CYP2D6, and can increase levels of drugs metabolized by these isoenzymes. CPY3A4 metabolizes about a quarter of all drugs.
MEDICAL CANNABIS DRUG INTERACTION STUDIES

- **Warfarin**
  - THC and CBD increase warfarin levels (Yamaori et al 2012).
  - Frequent cannabis use has been associated with increased INR.

- **Alcohol**
  - Alcohol may increase THC levels (Hartman 2015).

- **Theophylline**
  - Smoked cannabis can decrease theophylline levels (Stout and Cimino 2014).

- **Indinavir or nelfinavir**
  - Smoked cannabis had no effect (Abrams et al 2003).

- **Docetaxel or irinotecan**
  - Cannabis infusion (tea) had no effect (Engels et al 2007).

- **Clobazam**
  - In children treated with CBD for epilepsy, CBD increased clobazam levels (Jeffrey et al 2015).
MEDICAL CANNABIS CARDIOVASCULAR

- THC can cause tachycardia; chronic users may develop bradycardia.
- Cannabis can cause changes in blood pressure.
  - High doses can cause orthostatic hypotension and syncope (Handbook on Cannabis 2015).
  - Cannabis can cause an acute increase in blood pressure (Frost et al 2013).
- Cannabis can increase the risk of angina (Frost et al 2013).
- Rarely marijuana can trigger an acute myocardial infarction (Mittleman et al 2001).
- In patients who have had a myocardial infarction, an 18-year follow up study showed no conclusive evidence that smoking marijuana increased mortality (Frost et al 2013).
- Case reports have associated cannabis use with acute coronary syndrome, arrhythmias, sudden cardiac death, cardiomyopathy, transient ischemic attack, stroke (Thomas et al 2014, Jouanjus 2014).
MEDICAL CANNABIS SAFETY

“Medical cannabis used for chronic pain over one year appears to have a reasonable safety profile (199 Patients; no difference in risk of serious adverse events).”


“0% of patients surveyed after one year reported a ‘Great deal of Negative Physical Side Effects. 0% reported a ‘Great Deal of Negative Mental Side Effects0 (241 Patients, 12 months)”

START LOW, GO SLOW
THERAPEUTIC WINDOW
OPIOIDS and the brain

- Opiate μ receptors affect medullary and pons respiratory drive centers
- What other receptors also affect brainstem drive?
  - Benzodiazepines (GABA)
  - Alcohol (GABA)
- Apnea may result
  - High opiate dose alone
  - Synergistic combination of opiates with alcohol or benzodiazepines
HOW do we compare to other countries

How does hydrocodone demand in the US compare to other nations?

- Demand in Britain, France, Germany, Italy (combined population 264 million persons):
  3,237 grams a year

- Demand in US (population 319 million persons):
  27,400,000 grams a year

(Manchikati, Pain Physician, 2012)
Nsaids

“At least 16,500 NSAID-related deaths occur each year among arthritis patients alone…”

16,651 deaths occurred in 2010 from opiate prescription overdoses
Source: CDC MMWR, Mar 2013
CANNABIS USE DISORDER

Dependence Rates
National Institute on Drug Abuse

32%
23%
17%
15%
9%
9%

Tobacco
Heroin
Cocaine
Alcohol
Caffeine
Cannabis

SOURCE: Bostwick, 2012 (reference list).
Summary

- Cannabis does not kill patients (no case of death from marijuana overdose has ever been reported)
- Medical cannabis is has been shown to be effective for the treatment of chronic pain
- Neuropathy has the highest quality evidence
- Medical cannabis has a very well-tolerated side effect profile
- Medical cannabis works synergistically with opioids
- The medical community should be a pillar of education and support surrounding medical cannabis/ECS
Thank you. (Questions)
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