MEDICAL MARIJUANA FOR IBD: HOPE OR HYPE?

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Objectives

• Outline complexities of marijuana pharmacology and administration
• Review trial data related to inflammatory bowel disease
• Understand limitations in studying medical marijuana
• Review the current legal status of marijuana
• Questions
MARIJUANA AS MEDICINE
What is Marijuana?

- Marijuana refers to components of the *Cannabis* plant
  - Flowering buds of the female plants, harvested for their chemically-rich trichromes.
- *C. sativa*: Generally THC>CBD; used for hemp (minimal THC)
- *C. indica*: Higher relative CBD content
- Multiple hybrid strains on the market
Active Ingredients

- Marijuana contains over 400 chemical compounds including around 100 phytocannabinoids.
  - The most extensively studied to date include Δ⁹-tetrahydrocannabinol (THC), cannabidiol (CBD)
- Marijuana’s use dates to at least 2737 B.C. in China.
- Patent medicine for various GI diseases in the US.

Marijuana Pharmacology

- Phytocannabinoids bind to receptors on the body’s endocannabinoid system
- CB\textsubscript{1} found predominantly in the nervous system
  - Basal ganglia, cerebellum, hippocampus, neocortex, hypothalamus, and limbic cortex.
- CB\textsubscript{2}
  - Found predominantly on immune cells, spleen, GI tract
- THC
  - Acts as a partial CB\textsubscript{1} agonist and lesser degree partial CB\textsubscript{2} agonist
- CBD
  - Activates TRPV1, inhibits COX-1/2
  - Low affinity for CB\textsubscript{1} or CB\textsubscript{2}, possible inverse agonist

Gastroenterology 2017;152:415-429
Izzo Gut (2008) 57:1140-1155
## Marijuana Delivery Systems

<table>
<thead>
<tr>
<th>Marijuana Delivery Systems</th>
<th>“Joint/Blunt”</th>
<th>“Bowl”</th>
<th>“Bong”</th>
<th>“Vaporizer or Dabs”</th>
<th>Oils/ “Edibles”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How it Works</strong></td>
<td>MJ rolled in cigarette paper/cigar wrap</td>
<td>Metal, wood, or glass pipe</td>
<td>Smoke filtered through water</td>
<td>MJ heated to just below combustion</td>
<td>Ingested without burning; topical. Variable strength.</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Higher possible carcinogens to THC</td>
<td>Similar effect to joint/blunt</td>
<td>Cooled smoke. Reduced cannabinoids(?)</td>
<td>Higher THC, less carcinogen</td>
<td>No combustion products. Variable kinetics</td>
</tr>
</tbody>
</table>
Marijuana Pharmacokinetics

- Varied strengths (THC from <0.2% in hemp to 30%+ in oils/hashish)
- CBD (and other cannabinoid) interactions
  - CBD functions to reduce “high” sensation

<table>
<thead>
<tr>
<th>THC</th>
<th>Smoked MJ</th>
<th>Edible MJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>10-25%</td>
<td>5-20%</td>
</tr>
<tr>
<td>Time to peak effect</td>
<td>5-20 min</td>
<td>2-4 hrs</td>
</tr>
<tr>
<td>Duration</td>
<td>Dose-dependent (2hr)</td>
<td>4-6 hrs</td>
</tr>
</tbody>
</table>
MARIJUANA AND IBD
Epidemiology

Interest in IBD

• Patients with inflammatory bowel disease commonly use marijuana for relief of symptoms
  – Two recent survey studies (583 patients)
    • 12-16% of respondents reported active marijuana use
    • 48-51% reported having ever used marijuana in the past
    • Half of those who never used marijuana interested in using marijuana for abdominal pain if it were legal
    • Use was more common with history of abdominal surgery, chronic analgesic use, CAM use
Data on Symptoms

• 2001 meta-analysis evaluated 30 randomized controlled trials (1366 patients) from 1975-1997 comparing synthetic cannabinoids and placebo or standard antiemetic agents for chemotherapy-induced nausea and vomiting
  – Cannabinoids more effective than standard antiemetics or placebo
• A subsequent RCT involving 61 patients receiving moderately to highly emetogenic chemo
  – Dronabinol 10mg found to be equivalent to 16mg ondansetron for CINV
  – No benefit of combination therapy
• Similar data for appetite stimulation, pain modulation with synthetic cannabinoids

Tramer BMJ (2001) 323:16-21
Studies in IBD

• Marijuana use
  • Reduced symptom severity, need for steroids, and surgery (retrospective study)
  • Improvement in QOL, symptom severity, and weight gain of 8-10lbs (prospective observational study)
  • 5x higher risk of needing surgery (prospective survey study)
• Hospitalized patients
  – Less likely to need surgery, shorter hospital stay, fewer fistulae / abscesses, less TPN
    » More associated psychiatric disease
# Human Studies in IBD

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>IBD</th>
<th>Number</th>
<th>Product</th>
<th>Safety</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naftali²⁸</td>
<td>2011</td>
<td>Israel</td>
<td>Retrospective Observational</td>
<td>CD</td>
<td>30</td>
<td>Oral or Inhaled Cannabis</td>
<td>Not reported</td>
<td>Improvement in disease activity (&gt;=4 point reduction in HBI score). A reduction in need for other medications</td>
</tr>
<tr>
<td>Lahat²⁹</td>
<td>2012</td>
<td>Israel</td>
<td>Prospective Observational</td>
<td>CD and UC</td>
<td>13</td>
<td>50 g dry processed cigarettes per month</td>
<td>Not reported</td>
<td>Improvement in quality of life scores and disease activity indices (HBI)</td>
</tr>
<tr>
<td>Naftali³⁰</td>
<td>2013</td>
<td>Israel</td>
<td>Prospective Placebo Controlled Trial</td>
<td>CD</td>
<td>21</td>
<td>Cigarettes containing 115 mg THC twice daily</td>
<td>No difference in adverse effects between groups</td>
<td>No difference in clinical remission. (CDAI score &lt;150) Benefits in clinical response (decrease in CDAI of &gt;100) and steroid use. Improvement in symptoms (sleep and appetite)</td>
</tr>
<tr>
<td>Naftali³¹</td>
<td>2017</td>
<td>Israel</td>
<td>Prospective Placebo Controlled Trial</td>
<td>CD</td>
<td>19</td>
<td>Oral CBD 10 mg twice daily</td>
<td>No difference in adverse effects between groups</td>
<td>No beneficial effects in IBD. [Decrease in CDAI &gt;70] Safe and well tolerated</td>
</tr>
<tr>
<td>Irving³²</td>
<td>2018</td>
<td>United Kingdom</td>
<td>Double Blind placebo controlled, Parallel-group</td>
<td>UC</td>
<td>60</td>
<td>Oral capsule containing 50 mg CBD rich botanical extract taken twice daily</td>
<td>Higher mild-moderate adverse effects in treatment group (90% versus 48% in placebo)</td>
<td>Not effective in inducing remission. [Mayo score of &lt;=2 with no sub score &gt;1] Improved quality of life and global impression of change scores.</td>
</tr>
</tbody>
</table>

CBD, cannabidiol; CD, Crohn’s disease; CDAI, Crohn’s Disease Activity Index; HBI, Harvey-Bradshaw Index; IBD, inflammatory bowel diseases; THC, Δ⁹-tetrahydrocannabinol; UC, ulcerative colitis.
Studies in IBD

• A retrospective observational study in 30 patients with CD using MMJ
  – Significant decreases in Harvey Bradshaw index
    • HBI includes general well-being, abdominal pain, liquid stools, extraintestinal symptoms, abdominal inflammation on exam
  – Improved of well-being
  – Decrease in prescription medications, including steroids

• A subsequent prospective observational survey study in 13 Israeli CD/UC patients pre/post MMJ use for 3 months demonstrated:
  – Improvement in self-reported health perception, social functioning, ability to work, physical pain, and depression.
  – Harvey-Bradshaw index scores were significantly improved
  – Patients were noted to gain 4.3+/- 2kg during the treatment period
Trials in Crohn’s Disease

- 2013 RCT in 21 Crohn’s patients with at least moderate disease, refractory to standard therapy. Treated with joints bid (115mg THC (23%) and <0.5% CBD) or placebo (ethanol extraction)
  - Complete remission noted in 45% of tx group vs. 10%
  - Clinical response 90% vs 40%
  - Three patients in the tx group were able to stop steroids, two patients stopped opiate use
  - No significant change in CRP was seen
    - Baseline IBD group CRP was 1.4.
Trials in Crohn’s Disease

• RCT of low-dose cannabidiol (CBD) 10mg twice daily vs. placebo for 8 weeks in 20 moderately active CD patients failing standard therapy.
  • No improvement in CDAI between groups.
  • No change in LFTs, hemoglobin, albumin
  • No increased side effects compared to placebo
Trials in Ulcerative Colitis

• Ulcerative colitis
  – Placebo-controlled RCT in 28 patients with moderately active UC, not responding to traditional therapy
    • Twice daily marijuana cigarettes vs. placebo for 8 weeks
    • Significant improvement in disease activity index and endoscopy
      – No change in inflammatory markers
    • Improved appetite, behavior, pain, general satisfaction
    • Side effects: Memory decline and dizziness

Naftali, T, et al. DDW 2018 Abstract Sa1744
Trials in Ulcerative Colitis

- Ulcerative colitis
  - Placebo controlled RCT in 60 patients with mild to moderate UC on stable mesalamine therapy. 50mg CBD-rich cannabis botanical extract or placebo for 10 weeks.
    - No significant difference in end of treatment remission rates (28% vs. 26%)
    - Side effects in 90% of treatment group vs. 45% placebo
      - Dizziness
    - Improvement in Mayo score, SGA, QOL, and impression of change favoring CBD extract
Marijuana Research Summary

• Crowd acceptance of marijuana
  – Majority of the US in favor of legalizing in some capacity
  – 33 states with legal MMJ
  – Increased use with scientific and medical data limited
    • Opposite the FDA drug approval process

• Study of marijuana has been challenging
  – Legal hurdles (Schedule I drug with DEA)
  – Multiple strains, multiple modes of consumption, complex pharmacology, incomplete understanding of the molecular biology
Marijuana Research Summary

• Small IBD studies
  – Symptomatic improvements
  – No definitive demonstration of anti-inflammatory effect
  – Generally safe
  – Recommended as complementary therapy if used

• Future direction
  – Synthetic cannabinoids with gut-specific effect?
  – Strain-specific disease effects
Crohn’s and Colitis Foundation Position

• Updated November 2018
  – Cautions on limited evidence base at present and need to consider federal and state laws as well as employer’s policies.
  – “Supports policy changes that facilitate the conduct of clinical research and the potential development of cannabinoid-based medications, including further consideration for revising marijuana’s status as a federal Schedule I controlled substance”
Medical Marijuana Health Consultants
Loraine Glaser-Zakem, MD, ABIM
It's NOT Your Father's Marijuana
Professional Disclosures
I have no actual or potential conflict of interest in relation to this program/presentation.
What is medical marijuana?

The use of phytocannabinoids (plant-derived cannabinoids) to modulate our own endocannabinoid system (ECS)
This is NOT medical use!
Is it effective?

A 2017 comprehensive study by the National Academy of Sciences, Engineering, and Medicine revealed:

CONCLUSIVE evidence
a) benefit for chronic pain
b) antiemetic for chemotherapy-induced nausea and vomiting and
c) improvement in multiple sclerosis spasticity

MODERATE evidence improvement in sleep, fibromyalgia
MEDICAL CANNABIS CURRENT 21 QUALIFYING DIAGNOSES
FOR OHIO-JUNE 15, 2019

- PAIN-CHRONIC/INTRACTABLE
- FIBROMYALGIA
- SICKLE DISEASE
- PTSD (POST NATURAL STRESS DISORDER)
- INFLAMMATORY BOWEL DISEASE
- CANCER
- GLAUCOMA
Is medical marijuana safe?

Reuter's Health Nov. 2019:
Alcohol-related deaths and liver disease increasing.
- Opioid crisis
- Cigarette anyone? Cannabis has NOT been linked to development of COPD, asthma or lung cancer.
Contra-indications:

- Pregnancy (low birth weight, developmental delays)
- Age <21 years (developing brain)
- Possibly history of schizophrenia with psychosis (high dose THC)
Is medical marijuana safe?

- It is impossible to overdose on cannabis - no effect on respiratory center
- Not physically addicting - deposition in body fat slowly releases over time
- Worst-case scenario: unpleasant experience, dysphoric 6-8 hours
Editorial cartoon: DEA threatens marijuana docs

By Dan Wasserman. June 12, 2014. 5:29 p.m.

OK, DOCS- STEP AWAY FROM THE MILDLY PSYCHOACTIVE WEED...

... OR LOSE YOUR LICENSE TO PRESCRIBE HIGHLY ADDICTIVE AND SOMETIMES DEADLY OPIOIDS!!

Medical Marijuana Dispensary
Minimal Drug Interactions

Mostly CBD related due to competition for liver enzyme pathway (warfarin-like blood thinners, antifungals, some anticonvulsants)
Vaping

Not currently recommended due to risk of lipoid pneumonia which affects lung lubricant, vitamin E acetate present in 48/51 lung tissue samples.
Potential Adverse Effects:

- Marijuana/cannabis hyperemesis syndrome- unclear etiology
- THC in high doses may precipitate psychosis in those with prior history
- Unpleasant "dissociative" state, paranoia, difficulty focusing (THC, not CBD)
Dosing

Dosing is imperfect at best; so many variables, including genetics, body fat, diet.
Strains/Varieties:

- Sativa
- Indica
- Hybrids
Importance of CBD and its RATIO to THC

- CBD potentiates THC's anti-inflammatory effects
- Helps ameliorate THC "high" (CBD does not stimulate receptors in frontal lobe)
- Mediates sense of well being, pleasure and craving (hypothalamus)
Studies show decrease in:

- Opioids and other pain medications
- Anxiety medications
- Sleep medications
- Also decrease in alcohol use and decrease alcohol related MVAs where MMJ legalized
Current Legalities

- Cannot cross state lines with mj (Federal law)
- Forfeit permit to carry concealed weapon
- Several states reciprocate for medical mj
- Laws vary state to state (grow your own, accepted diagnoses)
How do I go about getting medical marijuana?

- 21 Qualifying Diagnoses
- See a physician who has CTR (Certificate to Recommend) to register with state
- State fee of $50, good for one year
Dispensaries: How do they work??