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ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.

MOC QUESTION

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Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.
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Managing IBD: Technology Enabled, Resilience-Based Self-Management Solutions (sponsored by GI OnDEMAND)
Faculty: David T. Rubin, MD, FACG; Laurie A. Keefer, PhD, and Megan Riehl, PsyC
At Noon and 8pm Eastern

Week 5 – Thursday, February 2, 2023
Exploring Gender Diversity in GI
Faculty: Asmeen Bhatt, MD, PhD, FACG; Millie D. Long, MD, MPH, FACG; and Allison R. Schulman, MD, MPH
At Noon and 8pm Eastern

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Disclosures

Linda Nguyen, MD
Alnylam: Consultant (Terminated, August 1, 2021); Ardelyx: Consultant; Eli Lilly Pharmaceuticals: Consultant (Terminated, November 1, 2021); Evoke Pharma: Consultant; Gemelli Biotech: Consultant; Neurogastryx: Consultant; Pendulum: Consultant; Phathom Pharmaceuticals: Consultant; RosVivo: Consultant; Salix Pharmaceuticals: Consultant; Takeda: Consultant

Steven Carpenter, MD, FACG
Dr. Carpenter has no relevant relationships with ineligible companies.

*All of the relevant financial relationships listed for these individuals have been mitigated

Cannabis for Gastrointestinal Disorders: Everything You Wanted to Know, But Were Afraid to Ask

Linda Nguyen, MD
Clinical Professor
Stanford University
Objectives

- Review the Endocannabinoid system & role of cannabinoids in GI disorders
- Discuss the prevalence of marijuana use in digestive diseases
- Explore the risks and benefits of medical cannabinoid use
- Form a framework for discussing cannabis use with patients

Our Patient

- 24 yo Female
- CC: N/V, postprandial abdominal pain, bloating and constipation. Can’t eat b/c of symptoms
- Symptoms > 5 years but increased past 2 yrs after flu-like illness
- PMH:
  - Asthma
  - Food allergies: hives with shellfish, nuts, milk
  - Migraines
  - EDS
  - POTS
  - Hip dislocation
- SH: no tobacco, no EtOH, occ marijuana, former ballet dancer
- FH: mother with migraines
Patient #1

- Structural evaluation: CT abdomen/pelvis, abdominal ultrasound, EGD, colonoscopy, all normal
- Normal labs: metabolic panel, TSH, ANA, ESR, cortisol paraneoplastic Ab panel, GAD ab
- Abnormal Labs: Hgb: 10.1, Ferritin 6
- EKG: sinus tachycardia
- Wireless capsule motility testing:
  - GET 6:15 (Normal: 0.5-5 hours)
  - SBTT 3:24 (Normal: 2.5-6 hours)
  - CTT 70:21 (Normal: 5-59 hours)

Follow up History

- Diagnoses:
  - Gastroparesis
  - Slow transit constipation
- Abdominal pain better on duloxetine (Cymbalta)
- N/V and constipation worse
- “Occasional marijuana use” recreationally
  - Patient has been using MJ 1-3x per day for the past 2 years for migraines, nausea and sleep

➤ Patient wants to know if she should continue using marijuana
Anatomy of Cannabis

- Marijuana has > 70 phytocannabinoids
- The bud (cola) contains trichomes (cannabinoids) & terpenes (essential oils)

<table>
<thead>
<tr>
<th>Cannabis Strains &amp; Components</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrahydrocannabinol (THC)</td>
<td>Psychoactive</td>
</tr>
<tr>
<td>Cannabidiol (CBD)</td>
<td>Not psychoactive</td>
</tr>
<tr>
<td>Cannabis indica</td>
<td>Calming (THC &gt; CBD)</td>
</tr>
<tr>
<td>Cannabis sativa</td>
<td>Energizing (THC &gt;&gt;&gt; CBD)</td>
</tr>
<tr>
<td>Cannabis ruderalis</td>
<td>Minimal THC, used to create hybrids</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Oral</th>
<th>Intranasal</th>
<th>Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset (minutes)</td>
<td>60-180</td>
<td>15-45</td>
<td>variable</td>
</tr>
<tr>
<td>Duration (hours)</td>
<td>6-8</td>
<td>6-8</td>
<td>variable</td>
</tr>
</tbody>
</table>

The Growth of Mainstream Marijuana

- Medical cannabis legal in 33 states plus the District of Columbia
Cannabis Use Increasing in the US with Decreased Perception of Risks

- Cannabis use increased from 4% in 1991-1992 to 9.5% by 2012-2013
- Prevalence greatest in young adults aged 18-25 (F: 25%; M: 27%)


Marijuana Cost & Quantity

https://americanmarijuana.org/medical-marijuana-statistics/
Medical vs. Recreational Cannabis

- Legal Age: Medicinal (18+) vs. Recreational (21+)
- Higher sales tax
  - Recreational = 23-38% tax: 15% MJ + 7.25% retail + municipal (0-15%) sales tax in CA
  - Medicinal = not subject to retail sales tax
- Access to more dispensaries
- CBD > THC

Eligible Medical Conditions (California):
- AIDS
- Anorexia
- Arthritis
- Cachexia
- Cancer
- Chronic pain
- Glaucoma
- Migraine
- Severe nausea
- Persistent muscle spasms (ie. MS)
- Seizures


Endocannabinoid System and the Gut

- Endocannabinoids
  - 2-arachidonoylglycerol (2-AB) -> CB1 & CB2
  - Anadamide -> CB1 & TRPV1
  - THC -> partial agonist CB1 > CB2
  - CBD -> CB2

Sharkey, Wiley. Gastroenterol 2016;151:252-266
Chronic Stress, the Endocannabinoid System & the Brain-gut Axis

Sharkey, Wiley. Gastroenterol 2016;151:252-266

IBD
Increased epithelial CB2 expression in IBD

Role of Cannabis in Digestive Disorders and Function

Liver
CB1 increases lipogenesis, upregulated in alcohol liver dz
CB2 associated w insulin resistance, protects against fibrosis

Colon/Small Bowel
CB1 inhibits peristalsis in the small bowel & colon

Decrease colonic tone & motility in IBS
Possible acute pancreatitis
Decreases diarrhea, abdominal pain & improves appetite in IBD

Esophagus
THC & CB1 decreases ILER

Stomach
THC & CB1 inhibits peristalsis

Pancreas
CB1 fibrogenesis
CB2 protects against fibrosis

Adapted Goyal H et al. Eur J Gastroenterol Hepatol 2017; 29;135-143
Marijuana Use in Patients with Gastroparesis & CUNV

- Patients who used MJ had more severe symptoms and decreased QOL
  - 12% patients with gastroparesis or CUNV used marijuana
  - 51% of patients using marijuana used > 2 years
  - 47% were daily users
  - 81% users perceived benefit in relieving GP symptoms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Marijuana Use</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=447)</td>
<td>Yes (n=59)</td>
</tr>
<tr>
<td>Nausea subscore</td>
<td>2.1 + 1.4</td>
<td>2.7 + 1.4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.9 + 1.5</td>
<td>3.5 + 1.2</td>
</tr>
<tr>
<td>PAGI-QOL</td>
<td>2.6 + 1.2</td>
<td>2.2 + 1.2</td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>41.8 + 13.0</td>
<td>46.0 + 12.1</td>
</tr>
<tr>
<td>Trait anxiety &gt; 50 (severe)</td>
<td>118 (36.4%)</td>
<td>28 (47.5%)</td>
</tr>
</tbody>
</table>


Patient Perception of Antiemetic Efficacy

- Survey study of 153 patients with chronic nausea
- Efficacy of antiemetic rated (0-5)
  - Mean efficacy of all anti-emetics 1.73
  - Marijuana (2.75), ondansetron (2.64) and promethazine (2.46) perceived to be most effective
  - Neuromodulators had the worst performance
  - More severe nausea responded better to marijuana or diphenhydramine but not metaclopramide

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Zikos T et al. Dig Dis Sci 2020

American College of Gastroenterology
Cyclic Vomiting Syndrome vs. Cannabinoid Hyperemesis

- Stereotypic episodes of nausea/vomiting (+/- abdominal pain)
  - Sudden or acute onset (usual duration < 1 week)
  - Absence of vomiting between flares (other sx can be present)
  - > 3 discrete episodes in one year
- 76% have partial response to TCA
- Marijuana use associated with lack of response to TCA
- Cannabinoid hyperemesis
  - Marijuana use preceded onset of GI sx
  - Heavy MJ use = use > 4x/week for > 1 year
  - Minimum 4 week cessation required but can require > 6 months of cessation to determine if sxresolve to abstinence

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Responders N=115 (87.1%)</th>
<th>Nonresponders N=17 (12.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>52 (45%)</td>
<td>8 (47%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>102 (89%)</td>
<td>15 (88%)</td>
</tr>
<tr>
<td>Mean Age</td>
<td>34±4 (20-68)</td>
<td>32.5±3 (18-59)</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>22±2</td>
<td>21±1.5</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>28±3</td>
<td>27±2</td>
</tr>
<tr>
<td>Mean TCA dose</td>
<td>90 mg/day (25-250)</td>
<td>85 mg/day (10-250)</td>
</tr>
<tr>
<td>Psychological disorder</td>
<td>32 (10%)</td>
<td>6 (35%)*</td>
</tr>
<tr>
<td>Migraine HA</td>
<td>23 (20%)</td>
<td>7 (41%)*</td>
</tr>
<tr>
<td>Smoking</td>
<td>32 (28%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Chronic Marijuana use</td>
<td>25 (22%)</td>
<td>9 (53%)*</td>
</tr>
<tr>
<td>Chronic Narcotic use</td>
<td>17 (15%)</td>
<td>9 (53%)*</td>
</tr>
<tr>
<td>4 hour GES</td>
<td>7 ± 4 %</td>
<td>6 ± 3 %</td>
</tr>
</tbody>
</table>

Venkatesan T et al. Neurogastroenterol Motil 2019;31, suppl 2

Marijuana: Differing Physiology vs. Function

- Background
  - Cannabinoids thought to slow motility via CB1 receptor
  - Hemp seed can improve constipation in CIC
- Findings:
  - Recent MJ users more likely to be male, younger, depressed and use other substances (EToH, tobacco, heroin & cocaine)
  - Recent MJ use associated with 32% decreased odds of constipation (aOR 0.68)

THC for Disappoints in Phase 2 Study of Chronic Abdominal Pain

- THC vs. Placebo for chronic postsurgical abdominal pain or chronic pancreatitis
  - Cannabis sativa up to 8 mg TID x 49 days
- Similar reduction in Pain VAS at end of study 40% vs. 37% (p=0.901)
- Limitations: groups combined due to low enrollment (total n = 65)


Marijuana use Common in IBD

- Active MJ use increased from 12.3% in 2012 to 22.8% in 2017
- Younger age and presence of chronic abdominal pain associated with current MJ use
- MJ perceived to be highly effective in relieving symptoms

<table>
<thead>
<tr>
<th>Medicinal Users (n = 48)</th>
<th>Nonusers (n = 142)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>31.4 ± 10.2</td>
<td>41.4 ± 14.7</td>
</tr>
<tr>
<td>SBBQ score</td>
<td>4.4 ± 1.3</td>
<td>5.2 ± 1.2</td>
</tr>
<tr>
<td>CD, n (%)</td>
<td>34 (70.8)</td>
<td>82 (57.7)</td>
</tr>
<tr>
<td>Prior surgery, n (%)</td>
<td>27 (56.3)</td>
<td>52 (36.6)</td>
</tr>
<tr>
<td>Prior hospitalization, n (%)</td>
<td>38 (79.1)</td>
<td>95 (66.9)</td>
</tr>
<tr>
<td>Biological therapy, n (%)</td>
<td>21 (43.7)</td>
<td>56 (39.4)</td>
</tr>
<tr>
<td>Chronic abdominal pain, n (%)</td>
<td>34 (70.8)</td>
<td>45 (31.7)</td>
</tr>
<tr>
<td>Current narcotics, n (%)</td>
<td>10 (20.8)</td>
<td>10 (7.04)</td>
</tr>
</tbody>
</table>

Cannabis Induces Clinical Response but Not Complete Remission in Crohn’s Disease

- THC-rich cannabis (115 mg) smoked twice daily induced complete remission (CDAI< 150) in 45% (5/11) vs. 10% (1/10) of patients with Crohn’s disease after 8 weeks (p=0.43)
- CDAI reduction > 100: Cannabis 90% vs. Placebo 30% (p<0.05)

<table>
<thead>
<tr>
<th></th>
<th>Cannabis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>330 ± 105</td>
<td>373 ± 94</td>
</tr>
<tr>
<td>Week 8</td>
<td>152 ± 109*</td>
<td>306 ± 143*</td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>68</td>
<td>71</td>
</tr>
<tr>
<td>Week 8</td>
<td>86</td>
<td>79</td>
</tr>
</tbody>
</table>


Mixed Outcomes with Cannabis Use in IBD

- Cannabis does not induce remission in UC (n=29) or Crohn’s (n=21)
- Prevalence of colectomy lower in cannabis users with UC compared to nonusers (4.4% vs. 9.7%, p=0.01)
- Shorter LOS: 4.5 vs. 5.7 days, p < 0.007

Mbachi C et al. Medicine (Baltimore) 2019;98:e16551
Cannabis May Be Associated with Worse Prognosis in Crohn’s Disease

- NIS dataset 2010-2014
- Pros
  - Anemia, Colorectal cancer, Need for TPN
  - Shorter LOS and lower total costs
- Cons:
  - Fistulizing disease/intra-abdominal abscess, Hypovolemia, GI bleeding

### Table 2: Outcomes in Crohn’s disease with cannabis vs. no cannabis

<table>
<thead>
<tr>
<th>Complication</th>
<th>No cannabis (n=1,000)</th>
<th>Cannabis (n=5,000)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disposition of patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine</td>
<td>2,579 (85.9%)</td>
<td>2,610 (87.0%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Transfer to short term hospital</td>
<td>60 (1.7%)</td>
<td>45 (1.5%)</td>
<td></td>
</tr>
<tr>
<td>Other transfers (DVF, ICU, other facility)</td>
<td>56 (1.9%)</td>
<td>35 (1.2%)</td>
<td></td>
</tr>
<tr>
<td>Home health care</td>
<td>135 (5.3%)</td>
<td>161 (5.4%)</td>
<td></td>
</tr>
<tr>
<td>Against medical advice</td>
<td>135 (5.3%)</td>
<td>200 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>903 (30.1%)</td>
<td>767 (25.6%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>15 (0.5%)</td>
<td>38 (1.2%)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Fluid and electrolyte disorders</td>
<td>1,047 (34.9%)</td>
<td>1,052 (34.4%)</td>
<td>0.963</td>
</tr>
<tr>
<td>Active fistulizing disease or intra-abdominal abscess</td>
<td>177 (5.9%)</td>
<td>257 (8.6%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Strictureing diseases</td>
<td>374 (12.4%)</td>
<td>261 (8.7%)</td>
<td>0.079</td>
</tr>
<tr>
<td>Infectious obstruction</td>
<td>572 (19.9%)</td>
<td>614 (20.5%)</td>
<td>0.196</td>
</tr>
<tr>
<td>Unexplained lower gastrointestinal hemorrhage</td>
<td>89 (2.9%)</td>
<td>120 (4.0%)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>176 (5.9%)</td>
<td>162 (5.4%)</td>
<td>0.441</td>
</tr>
<tr>
<td>C. diff</td>
<td>74 (2.5%)</td>
<td>54 (1.8%)</td>
<td>0.075</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>96 (3.1%)</td>
<td>111</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Small intestinal and colorectal resection</td>
<td>197 (6.5%)</td>
<td>163 (5.2%)</td>
<td>0.489</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>173 (6.8%)</td>
<td>171 (5.7%)</td>
<td>0.923</td>
</tr>
<tr>
<td>Pancreatic necrosis</td>
<td>141 (4.7%)</td>
<td>91 (3.0%)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Length of stay (days, mean ± SD)</td>
<td>4.8 ± 5.3</td>
<td>4.2 ± 5.0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Total charges per admission</td>
<td>$52,189</td>
<td>$29,806</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

* P-value <0.05 indicates statistical significance. Cell counts <11 are indicated by * as per HCUP privacy guidelines. SME, skilled nursing facility ICU, intermediate care facility.


Hype, Hope or Hybrid: The Cautionary Tale of Medical Marijuana
Adverse Effects of Marijuana

- Acute
  - Anxiety
  - Psychosis
- Chronic use
  - Driving impairment
  - Impaired psychosocial development
  - Dependence
  - Withdrawal


Impact of Cannabis on Driving

- Cannabis with alcohol causes greater cognitive impairment than either alone

Cannabis Interaction with Medications

- THC and CBD interact with CYP liver enzymes

THC and CBD Impact on Medication Concentrations

http://rx.ph.lacounty.gov/RxCannabis0918#table2main

Cannabis Misuse Associated with Increased ED Utilization In GI a Tertiary GI Patient Population

- Characteristics associated with cannabis misuse
  - Comorbidities: Neuropathy, Any psychiatric disorder, Other substance misuse
  - GI disorder: GERD
  - Patients with FGIDs less likely to have cannabis misuse
- Cannabis misuse associated with 1.47 fold increased risk of ED use independent of Dx

Counseling Patients on Medical Marijuana Use

- **Start low dose and increase slowly**
  - Typical marijuana dose: 1-3 g/d (divided)
  - Typical CBD dose: 5-20 mg/d
  - THC dose > 20 mg increased risk of side effects
  - Use strains with lower THC:CBD ratios to minimize psychoactive side effects
Counseling Patients on Medical Cannabis Use

• **Cannabis can be a double edged sword**
  - Can improve symptoms (but data limited & mixed)
  - Optimal dosing & duration not known
  - Can delay motility & secretions
  - Is associated with poor response to TCAs in patients with CVS
  - Associated with greater risk for ED use
  - Long term, regular use associated with CHS
  - Associated with increased CD complications
  - Cumulative costs of chronic use

The Data is still lacking but makes sense

• Mode of consumption oral > inhaled may help mitigate side effects of cannabis
• Intermittent vs. chronic daily use
• Mixed effects in IBD
• Monitor for changes in mood (increased anxiety)
• Monitor for need to escalate dose of cannabis
  - May be a sign of dependence, tolerance or misuse
• Don’t inhale and drive
• Be careful mixing substances
Don’t Be Afraid to Ask About Cannabis Use

➢ Be open minded and non-judgmental
➢ Employ shared decision making
➢ Consider costs when recommending therapy
➢ Know the cannabis rules in your state

The answers are all out there, we just need to ask the right questions.

Questions?

Linda Nguyen, MD

Steven Carpenter, MD, FACG

*All of the relevant financial relationships listed for these individuals have been mitigated
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ACG GI Circle
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