Disclosures:

Speaker:
David J. Hass, MD, FACG
Dr. Hass has no conflicts of interest related to this talk.

Moderator:
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Advisory Board: Gemelli Biotech; Consultant: Eli Lilly, Takeda, Ironwood, Pendulum, Neurogastrx, Phathom, Alnylam; Research Grant Funding: Bold Health, Vanda

CAM Therapies and Medical Cannabis:
“High” Time to Consider?

David J. Hass, MD, FACG
Associate Clinical Professor of Medicine
Yale University School of Medicine
PACT Gastroenterology Center
WHAT IS COMPLEMENTARY AND ALTERNATIVE MEDICINE?

- Medical interventions not taught widely in medical schools
- Not generally available in U.S. hospitals
  - *But this is rapidly changing...*

Some examples....

- Relaxation techniques
- Herbal Medicine
- Massage therapy
- Chiropractic therapy
- Megavitamins
- Homeopathy
- Fecal microbial therapy
- Hypnosis
- Biofeedback
- Acupuncture
- Art therapy
- Energy healing
- Lifestyle diets
- Medical cannabis
Some demographics....

- Women > Men
- Caucasians > other ethnicities
- Age group of 35-49 years old reported highest rates
- Correlation between income level and CAM use
- Correlation between education level and CAM use

Cost of therapy

- Majority of patients who implement CAM pay out of pocket
- Estimated $30 billion dollars spent per year
- Estimated $35 billion dollars spent per year on supplements
- Exceeds total out of pocket expenditures for hospitalizations

Non-Disclosure

- Less than 40% of CAM therapies are reported to PCPs
- Danger of non-disclosure

Common conditions

- Neck and back problems
- Depression
- Anxiety
- **Digestive problems**
  - Arthritis
  - Allergies
- Headaches
- Fatigue
- Hypertension
- Terminal illness
- Chronic Pain
Which of the following has been reliably well studied for the treatment of nausea and emesis?

A. Ginger (*Zingiber officinale*)
B. Ayurvedic medicine
C. Homeopathy
D. Psyllium

- Ginger (*Zingiber officinale*)
  - Enhances GI motility and acts as a 5-HT3 receptor antagonist
  - RCTs demonstrate efficacy in postoperative, chemotherapy, morning sickness
  - *Medication interactions*

Irritable Bowel Syndrome

- Hypnotherapy has been proposed as an effective complementary therapy in the treatment of Irritable Bowel Syndrome. Through “gut-related imagery,” what percentage of patients report initial overall symptom improvement with this modality?

A. 10%
B. 40%
C. 60%
D. 80%

Supplements/Natural Products

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PROS</th>
<th>CONS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peppermint Oil</td>
<td>Improves global symptoms Commerially available (e.g. IBGard™ – non-prescription, ultrapurified peppermint oil)</td>
<td>Side effects: diarrhea, nausea, vomiting, allergic reactions, atrial fibrillation, dyspepsia, GERD</td>
<td>Acts by direct blockade of smooth muscle calcium channels (esophagus, distal stomach and duodenal bulb) Allosteric effect on 5-HT3 receptor Low quality of evidence</td>
</tr>
<tr>
<td>Turmeric</td>
<td>Improves symptom severity via anti-spasmodic effect Commerially available</td>
<td>Side effects: nausea, vomiting, fatigue, headache and diarrhea</td>
<td>Increases GI motility and activates hydrogen producing bacteria in the colon Very low quality of evidence</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Presumed analgesic effect</td>
<td>Many adverse effects including hepatotoxicity, hyperemesis and paradoxical exacerbation of abdominal pain, sedation</td>
<td>Not consistently available with variable dosing Very low quality of evidence</td>
</tr>
</tbody>
</table>

### Supplements/Natural Products

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PROS</th>
<th>CONS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloe Vera</td>
<td>Anti-inflammatory and analgesic effect and can also act as a laxative</td>
<td>Side effect: diarrhea</td>
<td>Dosing ranges from 1 tablespoon to 1/3 cup daily</td>
</tr>
<tr>
<td></td>
<td>Commercially available</td>
<td>Can decrease absorption of certain medications</td>
<td>Very low quality of evidence</td>
</tr>
<tr>
<td>STW-5 (Iberogast™)</td>
<td>Improves global symptoms and abdominal pain</td>
<td>Hepatoxicity, increased bleeding, altered absorption of medications</td>
<td>Promotes fundic relaxation and antral contraction</td>
</tr>
<tr>
<td></td>
<td>Commercially available</td>
<td></td>
<td>Very low quality of evidence</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Improves global IBS symptom severity</td>
<td>Side effects: abdominal pain and bloating</td>
<td>Restoration of normal intestinal permeability</td>
</tr>
<tr>
<td></td>
<td>Commercially available</td>
<td></td>
<td>Very low quality of evidence</td>
</tr>
<tr>
<td>Beberine</td>
<td>Improvement in diarrhea, abdominal pain and urgency</td>
<td>No reported adverse effects but may interfere with drug metabolism</td>
<td>Anti-nociceptive and anti-depressant</td>
</tr>
<tr>
<td></td>
<td>Commercially available</td>
<td></td>
<td>Very low quality of evidence</td>
</tr>
</tbody>
</table>


### Mind/Body

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PROS</th>
<th>CONS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Behavioral Therapy</td>
<td>Management of stress surrounding IBS symptoms</td>
<td>Could be costly, but some insurance will cover</td>
<td>Appropriate for patients who report that stressors make GI symptoms worse</td>
</tr>
<tr>
<td></td>
<td>One meta-analysis reported</td>
<td></td>
<td><em>High quality of evidence</em></td>
</tr>
<tr>
<td></td>
<td><strong>NNT of 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No reported adverse effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gut-directed hypnotherapy</td>
<td>Overall symptom improvement of 50-80%</td>
<td>Could be costly, but some insurance will cover</td>
<td>Mechanism of action unknown</td>
</tr>
<tr>
<td></td>
<td>One meta-analysis reported</td>
<td></td>
<td><em>Moderate quality of evidence</em></td>
</tr>
<tr>
<td></td>
<td><strong>NNT of 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No reported adverse effects</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Effect of Hypnosis on Systemic and Rectal Mucosal Measures of Inflammation in Ulcerative Colitis

Joel E. Mawdsley, M.D.,1 David G. Jenkins, M.D.,1 Marion G. Macey, Ph.D.,2 Louise Langmaid, M.D.,2 and David S. Rampton, Ph.D.1

Mindfulness Training Reduces the Severity of Irritable Bowel Syndrome in Women: Results of a Randomized Controlled Trial

Is Hypnotherapy Equally Effective Self-directed at Home vs. with a Therapist?

- “Long-term Follow-up of Gut Directed Hypnotherapy Self-Exercises at Home Using CD vs. Individual Therapy by Qualified Therapists In Children With Irritable Bowel Syndrome or Functional Abdominal Pain”

  - Non-inferiority
  - 144 patients from previous RCT
  - 5.8 years of follow up
  - 80% CD group vs. 83% iHT group reported relief
  - Supports the use of low cost home treatment that can be widely distributed

R. Rexwinkel et al. Netherlands DDW 2019 Abstract1608
Inflammatory Bowel Disease

Turmeric (*Curcuma longa*)

- Prevents formation of free radical species
- Decreases TNF alpha and IL-1β production
- Inhibits NF-κB activation
- Inhibits synthesis of pro-inflammatory prostaglandins and leukotrienes through inhibition of arachidonic acid pathway
**Turmeric (Curcuma longa)**

- Used in Indian and Chinese herbal medicine
- Prospective RCT of UC pts in remission (4.6% vs. 20.5% relapsed in turmeric vs. placebo)
- RCT of curcumin 3gm demonstrated that over 53% achieved clinical and endoscopic remission in conjunction with mesalamine

*Hanai et al. CGH 2006, Lang et al. CGH 2015.*

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**Curcumin Use in Ulcerative Colitis - Is it Ready for Primetime? A Systematic Review and Meta-Analysis of Clinical Trials - Chandan et al.” Abstract 1871, DDW 2019**

- “Meta-analysis of RCTs evaluating the efficacy of adjunctive therapy with curcumin in treating pts with UC
  - 380 pts total included
  - Overall pooled OR of 3.13 for clinical response
  - Overall pooled OR of 3.33 for endoscopic response
Highly Bioavailable Curcumin for Crohn’s Disease - RDBPCT

- 360mg daily vs. placebo or 12 weeks
- Mild to moderate CD pts (<180 CDAI <450)
- CDAI significantly improved at week 12 (149 vs. 210)
  p=0.005 in Theracumin® group
- Clinical remission in Theracumin® group at week 12 compared with placebo - 40% vs. 0%. (p=0.02)
- Endoscopic remission noted, but not statistically significant.

Bommelaer et al. Abstract 1716, DDW 2019

Turmeric (Curcuma longa)

- Safe even in high doses
- No evidence of mutagenicity or chromosomal damage
- Turmeric does exhibit an inhibitory effect on platelet aggregation
- Patients who are maintained on agents such as aspirin, clopidogrel, or ticlopidine should be closely monitored
Screening Anti-Fibrotic Agents: Exploration of Promising Therapies to Reduce or Reverse Intestinal Fibrosis in Crohn’s Disease

- Assessed novel anti-fibrotic agents’ effects on myofibroblasts stimulated with TGF-B
- Measured profibrotic markers expression after exposure to novel agent.
- Curcumin significantly reduced expression of every profibrotic measured (ACTA2, procollagen, tissue inhibitor metalloproteases.)

The History of Cannabis

- 1600 A.D. -> As trade routes expanded, cannabis made its way to Europe
- Rumored that Queen of England used hemp for maladies
- Colonization of America from England – hemp brought to the eventual United States
The History of Cannabis

- Marijuana Tax Act of 1937
- Controlled Substances Act (1970) – Schedule I
- National Commission on Marijuana (1972) - Nixon
- “Just Say No” Campaign - Nancy and Ronald Reagan
- California Compassionate Use Act (1996) – Prop. 215

Statistics

- 10.7% of individuals regularly use cannabis in U.S. age 15-64
- Up to 50% of IBD pts have used cannabis in their lifetime
- 50% of IBD pts report interest in cannabis trials

Eur J Gastro Hep 2011;23(10):891-896
Indications for Medical Marijuana

- Malignancy
- Glaucoma
- Parkinson’s Disease
- HIV/AIDS
- Epilepsy
- Spinal cord injury/Muscle Spasticity
- Cerebral Palsy
- Cystic Fibrosis
- Cachexia
- Wasting Syndrome
- Spinal cord injury
- PTSD
- Crohn’s Disease
- Ulcerative Colitis
- Intractable Seizure Disorder
- Terminal Illness
Sifting through the “weeds”

- Phytocannabinoids
  - Δ9-tetahydrocannabinol main component (THC)
  - Cannabidiol (CBD)
  - Up to 130 other phytocannabinoids (CBG, CBDa, THCa)

- Three main subspecies of Cannabis
  - Cannabis sativa (higher THC content)
  - Cannabis indica (couchlock)
  - Cannabis ruderalis (low THC content, allows flowering more quickly)

- Currently nearly 800 different Cannabis strains

Endocannabinoid System

- Two endogenous endocannabinoids
  - Anandamide
  - 2-arachidonoylglycerol (2-AG)

- Two receptors: CB1 and CB2

- CB1 expressed principally in the enteric nervous system of the gut (submucosal and myenteric plexus) and also on mucosal epithelium.
- CB2 mainly expressed on surface of immune cells
Endocannabinoid System – CB1

- CB1 modulates central functions including pain control, nausea/vomiting center.
- CB1 promotes inhibitory effect on motility and secretory function via reduced acetylcholine release.
- CB1 receptors seen on colonic epithelium and enhance wound healing.

Endocannabinoid System – CB2

- CB2 receptors are found on inflamed colonic epithelium.
  - *In vitro* evidence to suggest that activation of CB2 receptors inhibits TNF-α, IL-1, IL-8 and prostaglandin release.
- Evidence of cannabinoid receptor expression in injured liver and pancreas.
- Antifibrotic effect in liver, apoptotic and anti-proliferative effect on GI cancer cell lines.
Ways to ingest...

Edibles
Physiology – “The Buzz”

<table>
<thead>
<tr>
<th></th>
<th>Inhalation</th>
<th>Ingestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>1 minute</td>
<td>30-90 minutes</td>
</tr>
<tr>
<td>Peak</td>
<td>30 minutes</td>
<td>2-3 hours</td>
</tr>
<tr>
<td>Duration</td>
<td>2-3 hours</td>
<td>4-12 hours</td>
</tr>
</tbody>
</table>

Adverse effects

- Anxiety
- Psychosis
- Decreased fertility
- Hyperemesis Syndrome
- Withdrawal Syndrome (irritability, sleep disturbance, anorexia, depressed mood)
- Pancreatitis
Cannabis Hyperemesis Syndrome

- First described by Singh and Coyle in 2004 in Australia
- Hypothesis is that the TRPV1 receptors located in area postrema of medulla and skin are desensitized from chronic exposure to cannabis
- Leads to decrease in anti-emetic physiology
- Hot water may augment cutaneous TRPV1 receptor function and thus increase anti-emetic properties

The data.....

- Little clinical evidence demonstrating efficacy
- Majority of controlled human studies with synthetic cannabinoids – not medical marijuana
- 5 RCT on marijuana and GI disease
  - Appetite, HIV (2), cancer-related anorexia-cachexia, and Crohn’s disease
- Cannabis use common in IBD
  - 50% of IBD patients admit to marijuana use; 16-50% use it to control symptoms of IBD
- Improved symptoms and QOL in 2 small observational studies

Storr et al. Inflamm Bowel Dis 2014
Allegretti et al. Inflamm Bowel Dis 2013
Randomized “Placebo” Controlled Trial of Cannabis (THC) in Crohn’s Disease

- Inclusion: CD patients with CDAI>200 failing at least 1 therapy for CD (including mesalamines) (n=21)
- RCT of Δ9-tetrahydrocannabinol (THC)
  - Cigarettes with 115mg THC vs no THC
- Primary endpoint complete remission (CDAI < 150)

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>THC (n=11)</th>
<th>Placebo (n=10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission</td>
<td>45% (5/11)</td>
<td>10% (1/10)</td>
<td>0.43</td>
</tr>
<tr>
<td>Clinical response (CDAI↓ &gt;100)</td>
<td>90% (10/11)</td>
<td>40% (4/10)</td>
<td>0.028</td>
</tr>
</tbody>
</table>


What about data for UC?

- RDBPCT
- Once daily CBD rich extract for 10 weeks
- Active UC patients
- N = 60
- Adjunct to mesaline therapy
- Improved quality of life
- Failure of primary endpoint of remission

Irving et al. Inflamm Bowel Dis 2018
“Epidemiology, National Trends and Outcomes of Cannabis Use in Hospitalized Patients With IBD in US 2002-2014”

- Hospitalized IBD patients (both CD and UC) have increased prevalence of cannabis use
- Inpatient mortality lower with cannabis use
- Length of stay shorter -1/2 day (p<0.001)
- Lower rate of colectomy 2.8% v. 6.7% with cannabis (p<0.001)

Elkaftawy et al. Abstract 1800, DDW 2019

“The Association of Hepatocellular Carcinoma and Cannabis Use”

- To determine association between HCC and Cannabis use
- Identified patients with HCC and Cannabis use
- 996,290 patients identified vs. controls
- Cannabis users were younger, more males, higher % of HBV, HCV, Cirrhosis, tobacco use
- OR of HCC =0.58 (40% less likely to develop HCC) compared with controls

“Dude, what’s the law?”

- Still a Federal Schedule I substance
- State laws vary widely
  - Most states that allow for medical marijuana have systems to protect physicians
  - Conant vs. Walters – Ninth Circuit Court of Appeals
    - Permanent injunction
    - Supreme Court refused to hear
- “Cole Memo” - Obama administration stated that resources will generally not be used to prosecute individuals who comply with state marijuana law.
THE BUZZ Kill?...

Rescinded The Cole Memo

Regulation

- Medical Use Approved in 36 states, D.C., Guam, Puerto Rico and U.S. Virgin Islands
- Recreational Use in 15 states and D.C.
- Different states have different regulations and laws
All out of pocket expense for patients

Average $500/month spent per patient

2025 US revenue from marijuana sales is estimated to be **13 billion dollars**

Nationwide legalization of marijuana could generate up to $28 billion in tax revenues for federal, state, and local governments.
Cannabis: Biology, Society and Industry 2019

Syllabus: Plant Science 4190
Cannabis: Biology, Society and Industry
Resources

- Association of Cannabis Specialists
  - https://cannabis-specialists.org/
- United Patients Group
  - https://unitedpatientsgroup.com/

Conclusions

- Knowledge of CAM therapies is lacking amongst gastroenterologists both in training and in practice.
- Medical cannabis is an emerging modality that with large prevalence amongst GI patients, specifically IBD patients.
- Research is ongoing with phytocannabinoids and in vitro evidence and physiology is promising.
- A thorough knowledge base of CAM therapies will help us care for our patients in a more comprehensive and responsible manner.
References

References


Thank you for your attention.

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Questions?

Speaker:
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Moderator:
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CONNECT AND COLLABORATE IN GI

ACG & CCF IBD Circle
ACG Hepatology Circle
ACG Functional GI Health and Nutrition Circle
ACG Women in GI Circle

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