Complementary and Alternative Therapy in IBD and IBS

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Disclosures

• Research Support: NIH, Pfizer, Celgene, AbbVie, Roche/Genentech, Takeda, CCFA
Complementary and alternative therapy/medicines (CAMs)

- Diverse group medical and health care practices, and products that are not considered part of conventional medicine.
- Used by 30%–50% of patients with IBD\(^1\) and up to 50% in IBS\(^2\)
  - use in the US varies by location
- Physicians often have limited knowledge of CAMs
- Those more likely to used CAMs\(^2\)
  - side effects of or dissatisfaction with conventional therapies,
  - female gender,
  - higher education,
  - use by friends or relatives,
  - long-term progression of disease,
  - prolonged use of steroids

Complementary and alternative therapy/medicines (CAMs) – THE PROBLEMS

• Few studies have evaluated these therapies,
• Most have small sample sizes or are uncontrolled.
• Lack of quality control for herbal preparations
• IBS pts not divided into IBS-C, IBS-D, IBS-M

Thus:

• ACG Task force on IBS reported that CAM have not consistently demonstrated a strong positive outcome

Cannabis

- Classified as a Schedule 1 drug by the US federal government, meaning that it has no medical use and a high potential for abuse.
- Several states have legalized the medical use of marijuana, decriminalized possession, and allowed legal recreational use.

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The image shows a map of the United States highlighting the states where it's legal to smoke marijuana. As of Nov 10, 2016, laws in some states have not yet taken effect. Some states not highlighted allow limited medical marijuana access. Source: NY Times.
The endocannabinoid system includes the cannabinoid receptor 1 (CB1) and receptor 2 (CB2) expressed within the brain, gut wall, enteric nervous system, and CB2 is highly expressed in immune cell types (macrophages, dendritic cells, and B cells)¹

Psychologic effects are produced through CB1.

CB2-selective agonists that do not generate untoward psychotic effects are in development².

In animal models, CB activation attenuates experimental colitis, and CB2 activation reduced reactive oxygen species produced by intestinal epithelium and decreased production of nitric oxide in macrophages.

Cannabis

• Crohn’s Disease Observational Study (N=13): 3 months of marijuana use improved overall perception of health, social function, ability to work, reduced physical pain and depression, increased weight and reduced the Harvey–Bradshaw index scores from 11.36 ± 3.17 to 5.72 ± 2.68 (p = 0.001).¹

• A Crohn’s survey study (n = 313), Cannabis had been used by 17.6% of respondents, subjectively improved pain and diarrheal symptoms but was associated with a 5-fold increased risk of surgery.²

• Search of pubmed found no trials of cannabis in UC or IBS

Cannabis

Controlled trial of marijuana for Crohn’s:

21 patients CDAI > 200 were randomly assigned to:

- 2 marijuana cigarettes per day (115 mg THC) or cannabis placebo (marijuana plant after extraction of THC).

- The primary end point was clinical remission (CDAI score < 150 after 8 weeks. – NOT REACHED

- Clinical remission: 5 of 11 in the cannabis group (45%); 1 of 10 in the placebo group (10%; P = .43).

- Clinical response (decrease in CDAI score of >100): 10 of 11 subjects in the cannabis group (90%; 330 ± 105 to 152 ± 109) and 4 of 10 in the placebo group (40%; 373 ± 94 to 306 ± 143; P = .028).
Cannabis

Controlled trial of marijuana for Crohn’s:

Figure 1. CDAI scores in study and placebo groups before and after treatment.

Table 4. Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Placebo median (minimum–maximum)</th>
<th>Cannabis median (minimum–maximum)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleepiness</td>
<td>4 (3–4)</td>
<td>3 (1–6)</td>
<td>.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (3–4)</td>
<td>4 (1–4)</td>
<td>.3</td>
</tr>
<tr>
<td>Concentration</td>
<td>4 (4–5)</td>
<td>4 (4–7)</td>
<td>.3</td>
</tr>
<tr>
<td>Memory loss</td>
<td>4 (4–4)</td>
<td>4 (4–6)</td>
<td>.4</td>
</tr>
<tr>
<td>Confusion</td>
<td>2 (2–2)</td>
<td>2 (1–2)</td>
<td>.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (1–2)</td>
<td>2 (1–2)</td>
<td>.9</td>
</tr>
<tr>
<td>Positive side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>4 (3–4)</td>
<td>1 (1–2)</td>
<td>.001</td>
</tr>
<tr>
<td>Appetite</td>
<td>4 (4–4)</td>
<td>2 (1–4)</td>
<td>.008</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>7 (3–7)</td>
<td>1 (1–4)</td>
<td>.002</td>
</tr>
</tbody>
</table>

*On a scale from 1 to 7, where 1 = no effect; 7 = very strong effect.

*On a scale from 1 to 7, where 1 = very satisfied; 7 = very dissatisfied.
Curcumin

- Curcumin, the principal curcuminoid found in the spice turmeric.
- Anti-oxidant, anti-inflammatory, anti-microbial and anti-carcinogenic activities.
- Inhibition of proinflammatory transcription factors NF-kB, mitogen-activated protein kinase (MAPK), the JAK/STAT signaling pathways, and mTOR
- Stimulation of Nrf2 which binds to the antioxidant response element (ARE) resulting in induction of glutathione S-transferases (GSTs) and heme oxygenase 1 (HO-1)

Curcumin in Active Ulcerative Colitis

- Multicenter randomized, double-blind placebo-controlled trial
- 50 pts with active mild-to-moderate UC despite > 4g/d 5ASA
- Randomized to curcumin capsules (3 g/day, n= 26) or placebo (n=24) for 4 weeks with continued 5ASA.
- The primary outcome: clinical remission (SCCAI ≤2) at week 4.

![Graphs showing clinical response and remission rates at week 4](image)

Figure 1. Clinical response and remission rate at study end point at week 4.

Figure 2. (A) Endoscopic response and remission rate at study end point at week 4.

Curcumin

Turmeric Extract in IBS

- 500 volunteers were screened for IBS using the Rome II criteria. 207 pts with IBS were randomized.
- 72 or 144 mg of a standardized turmeric extract taken daily for 8 weeks. No placebo arm.
- IBS prevalence, symptom-related quality of life (IBSQOL) and self-reported effectiveness.

Significant improvements in IBSQOL scales of between 5% and 36% in both groups.

Omega-3 Fatty Acids (Fish oil)

- Humans evolved on a diet with an omega-6 to omega-3 FA ratio of about 1/1.
- Today’s Western diets have a ratio of 10/1 to 20–25/1, indicating that Western diets are deficient in omega-3 FA compared with the diet on which humans evolved and their genetic patterns were established.¹

Antagonizing AA metabolism is recognized as a key anti-inflammatory effect of n-3 PUFAs also:
- Decrease leukocyte chemotaxis,
- Decrease adhesion molecule expression
- Decrease production of pro-inflammatory cytokines
- Generate a class of anti-inflammatory compounds called resolvins.

Omega-3 Fatty Acids (Fish oil)

EPIC-1 and EPIC-2

• 363 and 375 patients with quiescent Crohn’s were evaluated in EPIC-1 and EPIC-2, respectively.
• Pts in remission (CDAI<150) were randomly assigned to 4 g/d of omega-3 FA or placebo for up to 58 weeks.
• No other treatments for Crohn disease were permitted.

Figure 2. Kaplan-Meier Estimates of the Time to Relapse in the Omega-3 Free Fatty Acids and Placebo Groups for EPIC-1 and EPIC-2
Omega-3 Fatty Acids (Fish oil)

- Studies in UC have largely been disappointing with the larger studies (N=61\(^1\) and N=64\(^2\)) showing no benefit in maintaining remission compared to placebo over 12 months observation.

- Unable to identify any controlled trials of omega-3 FAs in IBS.

- Dietary Omega-3 FAs did not reverse stress-induced visceral hypersensitivity in maternally separated rats\(^3\).

**Probiotics**

- **Live** microorganisms that have a beneficial impact upon the host beyond purely providing nutrition
- Important for development of a healthy immune system
- Many strains have anti-inflammatory capacity\(^1,2,3\)
- We don’t know what constitutes normal gut flora (bacteria, fungi, viruses)
- Internet search of “probiotics” returned 25,100,000 results
- Overwhelming number of probiotic products in the form of pills, drinks, granola bars, yogurts, fermented foods.
- Studies are few and most have small sample sizes or are uncontrolled.

Probiotics

• The British Dietetic Association 2016 probiotics in IBS report states: “Specific probiotic recommendations for IBS management in adults were not possible at this time. Advise that probiotics are unlikely to provide substantial benefit to IBS symptoms.”

• In Crohn’s disease, a 2014 meta-analysis found that probiotics provided no significant benefit.

• In UC, probiotics (VSL#3) significantly increase the remission rates in active UC (P = 0.01, risk ratio [RR] = 1.51).

Probiotics

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Probiotics</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Year</th>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M-H, Random, 95% CI</td>
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<tr>
<td>Bifidobacteria</td>
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<td></td>
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<tr>
<td>Kato 2004</td>
<td>4</td>
<td>10</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Furrie 2005</td>
<td>5</td>
<td>9</td>
<td>3</td>
<td>9</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>19</td>
<td>19</td>
<td>11.0%</td>
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</tr>
<tr>
<td></td>
<td>9</td>
<td>6</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Heterogeneity: $\tau^2 = 0.00$; $X^2 = 0.07$, df = 1 ($P = 0.79$); $I^2 = 0%$</td>
<td></td>
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<td></td>
<td>Test for overall effect: $Z = 0.99$ ($P = 0.32$)</td>
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</table>

E coli

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Probiotics</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Year</th>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M-H, Random, 95% CI</td>
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<tr>
<td>Rembacken 1999</td>
<td>39</td>
<td>57</td>
<td>44</td>
<td>59</td>
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<tr>
<td>Matthes 2010</td>
<td>20</td>
<td>46</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>103</td>
<td>70</td>
<td>26.1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>47</td>
<td></td>
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<td></td>
<td>Heterogeneity: $\tau^2 = 0.03$; $X^2 = 1.22$, df = 1 ($P = 0.27$); $I^2 = 18%$</td>
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<td>Test for overall effect: $Z = 0.07$ ($P = 0.95$)</td>
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</table>

VSL#3

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Probiotics</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Year</th>
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<tr>
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<td>Events</td>
<td>Total</td>
<td>Weight</td>
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<tr>
<td></td>
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<td></td>
<td>M-H, Random, 95% CI</td>
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<tr>
<td>Tursi 2004</td>
<td>24</td>
<td>30</td>
<td>37</td>
<td>60</td>
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<tr>
<td>Miele 2009</td>
<td>33</td>
<td>77</td>
<td>11</td>
<td>70</td>
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<tr>
<td>Sood 2009</td>
<td>31</td>
<td>71</td>
<td>23</td>
<td>73</td>
</tr>
<tr>
<td>Ng 2010</td>
<td>13</td>
<td>14</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Tursi 2010</td>
<td>7</td>
<td>14</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>206</td>
<td>232</td>
<td>62.8%</td>
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</tr>
<tr>
<td></td>
<td>108</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: $\tau^2 = 0.10$; $X^2 = 10.10$, df = 4 ($P = 0.04$); $I^2 = 60%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: $Z = 2.86$ ($P = 0.004$)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Total: 328 | 321 | 100.0% | 1.51 (1.10–2.06)

Total events: 176 | 133

Heterogeneity: $\tau^2 = 0.12$; $X^2 = 22.79$, df = 8 ($P = 0.004$); $I^2 = 65\%$

Test for overall effect: $Z = 2.58$ ($P = 0.010$)

Test for subgroup differences: $X^2 = 4.27$, df = 2 ($P = 0.12$), $I^2 = 53.1\%$

FIGURE 3. The subgroup analysis for the remission/response rates of different probiotics in inducing remission of UC.

Probiotics-UC

- Multicenter, randomized, double-blind, placebo-controlled trial of VSL#3, for the treatment of adult mild-to-moderately active UC
- 77 assigned to $3.6 \times 10^{12}$ CFU VSL#3 and 70 to placebo, twice daily for 12 weeks. Intention-to-treat analysis was performed.

![Bar diagrams showing the (A) number of patients with a decrease in UCDAI score of at least 3 points from baseline to week 12, (B) number of patients with a decrease in total UCDAI of at least 50% from baseline at week 6, (C) number of patients who attained remission (UCDAI < 3) at week 12, and (D) number of patients achieving mucosal healing (mucosal assessment score of 0) at week 12.](image)

**Probiotics-Pouchitis**

**VSL#3 for Prevention of Pouchitis Recurrence**

- 40 pts with chronic relapsing pouchitis (>3 relapses/yr)
- Treated with antibiotics for 1 months
- Randomized to VSL#3 6g/d or placebo for 9 months

Beneficial results seen in a trial to prevent initial episode of pouchitis.

Cochrane Review analyzed randomized controlled trials of prevention or treatment of acute or chronic pouchitis in adults who underwent IPAA for ulcerative colitis.

For chronic pouchitis, low quality evidence suggests that VSL#3 may be more effective than placebo for maintenance of remission.

For the prevention of pouchitis, low quality evidence suggests that VSL#3 may be more effective than placebo.

Peppermint oil has spasmolytic effects and has received a positive evaluation from the ACG IBS Task force\(^1\)

- Double blind placebo controlled trial\(^2\)
- 57 pts with IBS by Rome II criteria, with normal lactose and lactulose breath tests and celiac dz screening
- Treated with peppermint oil (two enteric-coated capsules twice per day or placebo) x 4 weeks.

![Graph showing total IBS symptoms score](image)

Fig. 1. Total IBS symptoms score (mean ± S.E.M.) before \((T_0)\), after 4 weeks of treatment \((T_4)\) with peppermint oil \((Pe)\) or placebo \((Pl)\) and after 4 weeks of wash out \((T_8)\). \((^*\) P < 0.05 vs. \(T_0\) (t-test); \((^\_\) P < 0.05 vs. placebo (Mann–Whitney U-test).

- Randomized double-blind placebo-controlled study (N=90)
- Subjects took one capsule of enteric coated, delayed-release peppermint oil or placebo three times daily for 8 weeks.

Table 3  Frequency and severity of abdominal pain or discomfort in patients receiving Colpermin or placebo throughout the study. (n(%))

<table>
<thead>
<tr>
<th>Abdominal pain or discomfort</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 4</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0 (0%)</td>
<td>9 (33%)</td>
<td>11 (41%)</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>Colpermin</td>
<td>0 (0%)</td>
<td>6 (18%)</td>
<td>14 (42%)</td>
<td>14 (42%)</td>
</tr>
<tr>
<td>Occasional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>17 (63%)</td>
<td>15 (56%)</td>
<td>10 (37%)</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>Colpermin</td>
<td>15 (46%)</td>
<td>18 (55%)</td>
<td>11 (33%)</td>
<td>14 (42%)</td>
</tr>
<tr>
<td>Persistent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>9 (33%)</td>
<td>3 (11%)</td>
<td>6 (22%)</td>
<td>14 (52%)</td>
</tr>
<tr>
<td>Colpermin</td>
<td>14 (42%)</td>
<td>8 (24%)</td>
<td>7 (21%)</td>
<td>5 (15%)</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Colpermin</td>
<td>4 (12%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

P<0.001

Iberogast® is a mixture of nine herbal plant extracts originally used for functional dyspepsia in Germany for > 30 yrs

- Double-blind, placebo-controlled, multi-center trial: N=203
- The main outcome variables were the changes in total abdominal pain and irritable bowel syndrome symptom scores.
- Iberogast was significantly better than placebo in reducing the total abdominal pain score (P = 0.0009); and the irritable bowel syndrome symptom score (P = 0.001) at 4 weeks.

There are many other herbal therapies, diets (Paleo, Gluten Free, FODMAP, Anti-inflammatory), hypnotherapy, acupuncture, cognitive behavioral therapy etc… that we not discussed. The references and reviews below provide a more thorough view.


