Probiotics and Alternative Approaches to Managing Irritable Bowel Syndrome

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Life Style including exercise and diet

- Probiotics
- Acupuncture
- Psychological Therapies
- Herbs including peppermint oil
Impact of Physical Activity on IBS

IBS-Severity Scoring System, IBS score

102 IBS

12 weeks of moderate-vigorous activity 3-5 times/week vs. usual care


Fermentable oligo-, di-, monosaccharides and polyols (FODMAPs)

High FODMAP Diets Induce Increased Breath Hydrogen and Symptoms in IBS Patients

- Single-blind crossover
- 15 healthy/15 IBS
- 2-days
  - high-FODMAP diet (50 g/d)
  - low-FODMAP diet (9 g/d)
- GI sx s and lethargy induced by high FODMAP diet in IBS but not control patients

Breath hydrogen production

Low-FODMAP Improves IBS Symptoms Compared to Control Diet

Staudacher HM, et al. J Nurt 2012;142:1510. *P<0.05
Gluten in IBS without Celiac Disease

Mean Change in Symptoms Over 6 Weeks

- Overall symptoms
  - Gluten (n=19): \( P = .047 \)
  - Placebo (n=15): \( P = .031 \)

- Bloating
  - Gluten (n=19): \( P = .031 \)
  - Placebo (n=15): \( P = .02 \ast \)

- Pain
  - Gluten (n=19): \( P = .02 \ast \)
  - Placebo (n=15): \( P = .001 \ast \)

*P-value for analyses at Week 1 and entire study period. Biesiekierski JR, et al. Am J Gastroenterol. 2011

PROBIOTICS

- Live, viable microorganisms that, when administered in adequate amounts, confer a health benefit on the host
- May be found in foods, supplements, or drugs
- Available as single-organism or combination products

Common Probiotics

- Bifidobacterium
  - B infantis 35624
  - B animalis DN-173010
- Lactobacillus
  - L salivarius UCC4331
  - L reuteri
  - L casei
  - L plantarum 299v
  - L rhamnosus GG
- Saccharomyces boulardii
- E coli Nissle 1917

Proposed Mechanisms of Probiotics

- Colonization resistance
  - Competitive exclusion
  - Slp
  - G
- Metabolic effects
  - Bacteriocins
  - Decrease pH
  - Quorum sensing
- Modulation of signal transduction
  - NF-κB
  - IFNγ
  - MAPK

Probiotics
- Enhance microbial flora
- Innate/Adaptive Immunomodulation
  - IgA, IgG, IgM
  - Increase mucin production
- Metabolic effects
  - Bacteriocins
  - Decrease pH
  - Quorum sensing
- Modulation of signal transduction
  - Enhance cytokines (IL-10, TGFβ)
  - PC

Probiotics for IBS: Clinical Considerations

- Health benefits are strain-specific and dose-specific
  - Each strain and dose must be tested to assess efficacy

- Probiotics in US are foods or dietary supplements
  - Not regulated as drugs
  - Claims regarding disease benefits not allowed on product label

Meta-analysis Probiotics in IBS

- 10 RCTs involving 918 patients with dichotomous outcomes

- Probiotics were statistically significantly better than placebo
  - NNT=4 (95% CI 3 to 12.5).
  - Significant heterogeneity ($\chi^2=28.3$, $p=0.001$, I²=68%)

- **Conclusion:** “Probiotics appear to be efficacious in IBS, but the magnitude of benefit and the most effective species and strain are uncertain”


### Efficacy of Probiotics in IBS: Dichotomous Data

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus (3 studies)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>36 / 70</td>
<td>55 / 70</td>
<td>26.88</td>
<td>0.64</td>
<td>(0.41, 1.02)</td>
</tr>
<tr>
<td>Combination (4 studies)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>69 / 151</td>
<td>103 / 151</td>
<td>37.23</td>
<td>0.66</td>
<td>(0.36, 1.20)</td>
</tr>
<tr>
<td>Bifidobacterium (2 studies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>156 / 300</td>
<td>75 / 122</td>
<td>23.66</td>
<td>0.80</td>
<td>(0.56, 1.13)</td>
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<tr>
<td>Streptococcus (1 study)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>20 / 32</td>
<td>19 / 22</td>
<td>12.23</td>
<td>0.72</td>
<td>(0.53, 0.99)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>281 / 553</strong></td>
<td><strong>252 / 365</strong></td>
<td><strong>100.00</strong></td>
<td><strong>0.71</strong></td>
<td><strong>(0.57, 0.88)</strong></td>
</tr>
</tbody>
</table>

**Bifidobacterium infantis 35624 for IBS**

Abdominal Pain/Discomfort

362 primary care IBS patients

![Graph showing symptom score improvement over weeks for different groups.

*Likert scale = 0 (none) to 5 (severe); treatment was stopped at 4 wks.*


**Bifidobacterium animalis DN 173 010 (B. regularis) for IBS**

Intention-to-treat population
N= 267

Patients with < 3 BM/wk
N=19

Guyonnet et al. *Aliment Pharmacol Ther.* 2007;26:476

Fermented milk product (Activia)
B. animalis 1.25 x 10¹⁰ CFU per serving
S. therophilus & L. bulgaricus
Multispecies Probiotic Mixture in IBS-D

7 species of probiotic bacteria:
  Lactobacilli acidophilus, plantarum, rhamnosus
  Bifidobacteri breve, lactis, longum
  Streptococcus thermophilus

One capsule B.I.D. x 8 wks (1.0×10¹⁰ cells/d)

n=50
Adequate Relief 50% of weeks
  48% probiotic vs. 12% placebo, P=0.01
Stool consistency: probiotics > placebo P<0.05
No effect on individual symptom scores

Ki Cho et al., J Clin Gastro 2012 Mar;46(3):220-7

Lactobacillus paracasei enriched artichokes for Chronic Constipation

A double-blind, randomized, crossover trial

- 20 CC pts randomized to 180 g ordinary artichokes vs. artichokes with L. paracasei (2×10¹⁰ CFU) x 15 days
- Improvements also reported for frequency, hard stools, and feeling of incomplete evacuation

Rizzio G. et al. Aliment Pharmacol Ther 2012;35:441
Probiotics for IBS: Summary

- Most studies are small, single-center
- Current evidence suggests that probiotics may be effective
- Best evidence to date is with B. infantis
- Further studies are clearly needed to assess dose, duration of the therapy and the appropriate patient

Complementary and Alternative Medicine (CAM) use is common in the USA

- Medical treatments not commonly considered to be a part of conventional medicine
- Between 1997-2002 ~ 35% of the population used CAM\(^1\)
- In an HMO clinic use of CAM was reported by ~ 35% of patients with FBD with an annual cost of $200\(^2\)
  - Women, higher education, anxiety

Acupuncture: Basic Principles

• Targets the state of ‘disharmony’, imbalance in the yin-yang and its connecting qi.

YinYang

Acupuncture: Basic Principles

• 365 traditional acupuncture points on 14 main channels (meridians)

• Each point has defined therapeutic actions

• 5-15 needles are used in a session; combinations varying during a course of sessions
Acupuncture: Basic Principles

• After puncturing the skin, needles are moved back & forth.

• Needles are left in place for 15-20 minutes.

Basic Theory: Acupuncture

• Other therapies commonly used during acupuncture treatment:
  – Massage
  – Cupping
  – Heat
  – Electrical stimulation
  – Scarification (counter irritation)
  – Lifestyle counseling
NIH Consensus Panel Recommendations for Acupuncture

- Efficacious for:
  - adult post-op and chemo induced nausea and vomiting
  - and probably for nausea of pregnancy
  - Post-op dental pain

- Quality or quantity of research evidence for other diseases are not sufficient to provide firm evidence

Specific Challenges in Performing Acupuncture Trials

- Inherent bias by the acupuncturist
- Matching sham control
  - Penetrating, non-penetrating, location
- Heterogeneity of acupuncture techniques
- Individuality of treatment according to ‘patterns of disease’ is difficult to incorporate into a RCT
- Non-specific effects
Acupuncture for IBS: Systematic Review and Meta-Analysis

- 17 RCTs (N=1,806)
- Heterogeneity: interventions, controls, and outcomes
- Sham-controlled RCTs have found no benefits of acupuncture relative to a credible sham acupuncture control on IBS symptom severity or IBS-related QOL.


Acupuncture IBS Clinical Trial

P=0.25


Note: Error bars indicate standard errors. None of the acupuncture—sham acupuncture differences are statistically significant.
**Acupuncture in IBS: Summary**

- Acupuncture/sham acupuncture are superior to Waitlist Control
  - Is sham acupuncture active therapy?
  - Non-specific (i.e., placebo) effects?

- Recent trials have shown acupuncture to have a small non-significant effect on IBS symptoms
  - ? If other therapies were added to acupuncture (e.g., cupping, electrical activation)
  - ? Subset of IBS
  - ? A larger trial (e.g., n=970) would be needed to adequately power a larger more definitive study

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**Psychological Therapies for IBS**
RCTs of psychological vs control therapy or “usual care” in IBS

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
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<tbody>
<tr>
<td>Ford A C et al. Gut 2009;58:367-378</td>
<td>5</td>
<td>10</td>
<td>1.50 (0.90-2.51)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Internet-Cognitive Behavioral Treatment vs. Stress Management for IBS

N=195
Improvement (ICBT): anxiety QOL Adequate Relief

Hypnosis in IBS

24 general practices in the UK
86 pts – failed initial therapy
5 30 min sessions of gut-directed hypnotherapy vs. usual care

Roberts et al. Br J Gen Pract. 2006 February 1; 56(523): 115

Hypnotherapy for IBS

• 4 studies (n=147) met inclusion criteria
  – 1 study (Whorwell, 1984): hypnotherapy vs. psychotherapy and placebo pill
  – 2 studies (Paulson, 2002; Galvoski, 1998) hypnotherapy vs. waiting-list controls
  – 1 study (Roberts, 2006) hypnotherapy vs. usual medical management.

• Hypnotherapy > waiting list control or usual medical management
  – abdominal pain, composite primary IBS symptoms
• AEs not reported in any of the trials.

• Quality was inadequate to allow any conclusion about the efficacy of hypnotherapy for IBS

Herbal Therapies for IBS

Peppermint Oil in IBS

• Obtained by steam distillation of the aerial parts of the flowering plant *Mentha piperita*
• Active ingredient: menthol (calcium channel blocking activity)
• Meta-analysis (1998)
  – 8 trials. 5 trials were DBPC
  – Significant (P<.001) global improvement of IBS
• A Subsequent RDBPC in Taiwan (n=110 IBS pts) x 4 weeks
  – Peppermint - < abd distention, stool frequency, and flatulence. 79% of the patients also had alleviation of abdominal pain.

Peppermint Oil Improves Abdominal pain/discomfort

90 IBS patients in Iran were randomized to enteric-coated, delayed-release peppermint oil (Colpermin) or placebo tid.

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 4</th>
<th>Week 8</th>
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</thead>
<tbody>
<tr>
<td><strong>None</strong></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><strong>Occasional</strong></td>
<td></td>
<td></td>
<td></td>
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</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>
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<tr>
<td><strong>Persistent</strong></td>
<td></td>
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</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>
</tbody>
</table>


Meta-analysis of Herbs in IBS

— Only 4 studies good quality

— “Herbal medicines should be used with caution. It is necessary to conduct rigorous, well-designed clinical trials to evaluate their effectiveness and safety in the treatment of IBS”

Herbs in IBS: TXYF

• Tong xie yao fang (TXYF)
  • rhizoma atractylodis macrocephalae, radix paeoniae alba, pericarpium citri reticulatae, and radix saposhnikoviae.

  – Meta-analysis 12 studies (2006)
    • TXYF > conventional therapies
  – Subsequently (2009)
    • TXYF (n=80) vs Miyarisan, a probiotic (butyric acid bacteria), (n=40) for 4 weeks
      • no significant difference
      • # activated mast cells decreased in the TXYF group


Herbs in IBS: STW 5

• bitter candytuft, chamomile flower, peppermint leaves, caraway fruit, licorice root, lemon balm leaves, celandine herbs, angelica root, milk thistle fruit.
  – STW 5-II: does not include angelica root and milk thistle fruit.
• Multi-center RDBPC with 208 IBS pts
  – STW 5, STW 5-II, bitter candytuft monoextract (BCT), or placebo for 4 weeks.

Herbs in IBS: Padma Lax

- Tibetan herbal formula:
  - dry extract of Aloe, calumba root, cascara, chebulic myrobalan fruit, condurango, elecampane, frangula bark, gentian root, ginger, heavy kaolin, long pepper, nux vomica, rhubarb, sodium hydrogen carbonate, and sodium sulfate.

- RDBPC IBS-C
  - Padma Lax significantly improved constipation, abdominal pain, incomplete evacuation, abdominal distension, and flatus/flatulence
  - AEs loose stools in a small number of subjects, but they responded well after lowering the dosage.

“Pure Relief in a Bottle”


Summary

- Lifestyle modifications, particularly exercise and dietary modification, may improve symptoms of IBS.
- CAM therapies may have a role in treating some patients with IBS.
- High quality multi-center studies placebo controlled trials are needed to further define this role.
- Side effects, particularly with herbs, need to be well characterized.