Evidence-based Treatment Strategies for IBS

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Rome III criteria for IBS

Recurrent abdominal pain or discomfort at least 3 days / month in the last 3 months associated with 2 or more of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form of stool

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Longstreth et al, Gastroenterology 2006; 130: 1480–91
IBS Subtypes Are Based on Stool Consistency

Adapted from Longstreth GF, et al. Gastroenterology. 2006;130:1480-1491

Management Options for IBS
Graded Treatment of IBS

- Psychological treatments
- Continuing care
- Improve functioning

+ Follow-up visit
+ Manage stress
+ Pharmaco therapy

- Diet, lifestyle advice
- Positive diagnosis
- Explain, reassure

Does exercise help IBS?
Impact of Physical Activity on IBS

**IBS-Severity Scoring System**

- 102 IBS pts by Rome II
- 12 wk intervention
- 20-60” moderate to vigorous activity 3-5 times/wk

*N = 38 N = 37*


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**Food and IBS Symptoms**

- 197 IBS pts (Rome III)
- Symptom severity correlates with number of food sensitivities
- No impact of IBS subgroup

Dietary Interventions for IBS: What is the Evidence?

Traditional Dietary Advice for IBS

- No standardized IBS diet
- Avoid:
  - Caffeine, chocolate, alcohol
  - Lactose, Sorbitol
  - Fatty or junk food
- Encourage:
  - Dietary fiber
  - Sufficient time in quiet setting for meals
What are FODMAPs?

- Fermentable oligo-, di-, monosaccharides and polyols
  - Fruits with fructose exceeding glucose
    - Apples, pears, watermelon
  - Fructan containing vegetables
    - Onions, leeks, asparagus, artichokes
  - Wheat based products
    - Bread, pasta, cereal, cake, biscuits
  - Sorbitol and lactose containing foods
  - Raffinose containing foods
    - Legumes, lentils, cabbage, brussels sprouts

Eswaran & Chey, GI Ci North Am 2011;40:141
Gibson & Shepherd. J Gastro Hepatol 2010;25:252

FODMAPs: Mechanism of Action

(Courtesy of Sue Shepherd, Ong, 2010, Barrett, 2009)
### Daily Symptom Scores on low-FODMAP vs. Control Diet

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Control</th>
<th>Intervention</th>
<th><em>P &lt; 0.05</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloating</td>
<td><img src="image1" alt="" /></td>
<td><img src="image2" alt="" /></td>
<td>*</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td><img src="image3" alt="" /></td>
<td><img src="image4" alt="" /></td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td><img src="image5" alt="" /></td>
<td><img src="image6" alt="" /></td>
<td></td>
</tr>
<tr>
<td>Bloating/diastasis</td>
<td><img src="image7" alt="" /></td>
<td><img src="image8" alt="" /></td>
<td></td>
</tr>
<tr>
<td>Urgency</td>
<td><img src="image9" alt="" /></td>
<td><img src="image10" alt="" /></td>
<td><img src="image11" alt="" /></td>
</tr>
<tr>
<td>Diarrhea</td>
<td><img src="image12" alt="" /></td>
<td><img src="image13" alt="" /></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td><img src="image14" alt="" /></td>
<td><img src="image15" alt="" /></td>
<td></td>
</tr>
<tr>
<td>Tiredness</td>
<td><img src="image16" alt="" /></td>
<td><img src="image17" alt="" /></td>
<td></td>
</tr>
<tr>
<td>Overall symptoms</td>
<td><img src="image18" alt="" /></td>
<td><img src="image19" alt="" /></td>
<td>*</td>
</tr>
</tbody>
</table>


### Pharmacologic Treatments for IBS

- **Bloating**
  - Probiotics
  - Antibiotics
  - Lubiprostone
  - Linaclotide

- **Diarrhea**
  - Loperamide
  - Antibiotics
  - Probiotics
  - Alosetron

- **Constipation**
  - Ispaghula/psyllium
  - Osmotic/Stimulants
  - Lubiprostone
  - Linaclotide

- **Abdominal pain/diastasis**
  - Antispasmodics
  - Antidepressants
  - Alosetron
  - Lubiprostone
  - Linaclotide

Brandt LJ, et al. Am J Gastroenterol. 2009; 104(Suppl.):S1
# Established & Emerging Therapies for IBS-D

**ACG IBS Task Force Evidence-Based Summary on Medical Therapies for IBS-D**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Global Sx</th>
<th>Pain</th>
<th>Urgency</th>
<th>Diarrhea Symptoms</th>
<th>Bloating</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber (psyllium)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>Loperimide</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>2C</td>
</tr>
<tr>
<td>Anti-spasmodics</td>
<td>+/-</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>2C</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>1B</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>1B</td>
</tr>
<tr>
<td>Alosetron</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>2A/1B</td>
</tr>
</tbody>
</table>

*ACG IBS Task Force. Am J Gastroenterol 2009;104 (suppl 1):S1-35*
Rifaximin for Global Improvement in IBS: A meta-analysis

<table>
<thead>
<tr>
<th>Measure Outcomes</th>
<th>Response rates (%)</th>
<th>Weight</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rifaximin</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharara</td>
<td>27.0</td>
<td>9</td>
<td>1.4%</td>
<td>18%</td>
</tr>
<tr>
<td>Pimental</td>
<td>32.5</td>
<td>9</td>
<td>1.6%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Lembo</td>
<td>52.3</td>
<td>44.2</td>
<td>25.2%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Target 1</td>
<td>40.8</td>
<td>31.2</td>
<td>34.9%</td>
<td>9.6</td>
</tr>
<tr>
<td>Target 2</td>
<td>40.6</td>
<td>32.2</td>
<td>36.8%</td>
<td>8.4</td>
</tr>
<tr>
<td>Overall</td>
<td>43.3</td>
<td>34.2</td>
<td>100%</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=5.26$, df=4 $I^2=24\%$ $p=0.26$

Menees et al. AJG 2012

Antibiotics for IBS: Points to Consider

- Reasons for symptom improvement unclear
  - SIBO vs. alteration of colonic flora/fermentation?
- Optimal diagnostic test for SIBO unclear
  - Breath test results may not predict response to antibiotics
- Optimal antibiotic therapy unclear
- Benefits appear transient
  - How can we increase the durability of response?
- Potential consequences of repeated, widespread antibiotic use?
5-HT₃ Antagonists for IBS

- 11 trials, 7216 patients
- Five studies recruited IBS-D only
- All 8 alosetron studies had a Jadad score ≥ 4

<table>
<thead>
<tr>
<th>5-HT₃ antagonist</th>
<th>% Improvement</th>
<th>RR of symptoms remaining (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT₃ antagonist</td>
<td>51</td>
<td>0.78 (0.71 – 0.86)</td>
<td>7 (5 – 11)</td>
</tr>
<tr>
<td>Placebo</td>
<td>36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Significant heterogeneity (I² = 80%); no funnel plot asymmetry

Ford AC et al. Am J Gastroenterol 2010; 104, 1831-1843

Safety Profile of Alosetron

- Black box warning: serious GI effects
- Ischemic colitis
  - 2 per 1000 patients over 3 months
  - 3 per 1000 patients over 6 months
- Constipation
  - Alosetron (1 mg bid), 29%
  - Placebo, 6%
- No clinically relevant drug-drug interactions
- Pregnancy category B

Alosetron package insert
Established & Emerging Therapies for IBS-C

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Global Sx</th>
<th>Pain</th>
<th>Bloating</th>
<th>Stool Frequency</th>
<th>Stool Consistency</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber (psyllium)</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>2C</td>
</tr>
<tr>
<td>Laxatives (PEG)</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>2C</td>
</tr>
<tr>
<td>Lubiprostone</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>1B</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>1B</td>
</tr>
<tr>
<td>Linaclotide</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

ACG IBS Task Force Evidence-Based Summary on Medical Therapies for IBS-C

PEG 3350 for IBS-C

- 27 adolescents with IBS-C
- Polyethylene glycol improved frequency of bowel movements but not pain

Brandt LG e al for the ACG Task Force on IBS. Am J Gastroenterol. 2009;104(suppl 1):S1-S35.

Polyethylene Glycol for IBS-C: Results from an RCT


N=143
*P<0.0001
Chloride Channels in Intestinal Transport

Enterocytes

H₂O
Na⁺
Cl⁻

CFTR Channel
Linaclotide
Plecanitide

Cl⁻/H₂O

Ion Transport

K⁺
Na⁺
K⁺

Cl⁻/2Cl⁻

Lubiprostone

Na⁺

Lubiprostone for IBS-C: Data from 2 Phase III Trials

Overall responder = monthly responder for at least 2 of 3 months
Monthly responder = at least moderate relief for 4/4 weeks or significant relief for 2/4 weeks

Drossman DA et al. Gastroenterology 2007; 132:639f

\[ n = 780 \]

\[ n = 387 \]
Incidence of Nausea with Lubiprostone in Clinical Trials

- Chronic idiopathic constipation: 24 mcg bid with food
- Irritable bowel syndrome with constipation: 8 mcg bid with food

![Incidence of Nausea with Lubiprostone in Clinical Trials](Image)


Linaclotide for IBS-C: MOA

- Minimally absorbed, 14-amino acid investigational peptide
- Guanylate cyclase-C (GC-C) agonist, results in generation of cyclic guanosine monophosphate (cGMP)
- Based upon available preclinical data, cGMP is proposed to have two activities:
  - **Intracellular**: activation of CFTR leads to increased luminal fluid secretion and intestinal transit
  - **Extracellular**: inhibition of pain fiber activity, which is thought to result in reduced visceral pain

![Linaclotide for IBS-C: MOA](Image)
Linaclotide Phase 3 IBS-C Trial

6/12 Week Responder Primary Endpoint

Composite Responder
(FDA Interim Endpoint)

≥30% abdominal pain reduction +
increase ≥1 CSBM from baseline; in
the same week

Composite Responder
(6/12 Week APC +1)

50%

% Responders

≥30% abdominal pain reduction +
increase ≥1 CSBM from baseline; in
the same week

Most common side effect Diarrhea 18% wks 1-12

Chey et al. Am J Gastroenterol 2012

Linaclotide Phase 3 IBS-C Trial

Abdominal Pain Over 26 Weeks

% Change Ab. Pain

Trial Week

p = 0.007 for Week 1
p < 0.0001 for Weeks 2-26

ITT Population, Observed Cases, LS-Means presented, p-values based on ANCOVA at each week. Bars represent 95% confidence intervals.

Chey et al. Am J Gastroenterol 2012
Centrally Acting Therapies for IBS

Antidepressants for IBS: Updated meta-analysis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs + SSRIs</td>
<td>64.9%</td>
<td>43.7%</td>
</tr>
<tr>
<td>(16 RCTs, n=1022)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCAs</td>
<td>62.2%</td>
<td>43.9%</td>
</tr>
<tr>
<td>(10 RCTs, n=682)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>69.4%</td>
<td>43.2%</td>
</tr>
<tr>
<td>(5 RCTs, n=356)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR=relative risk; SSRIs=selective serotonin reuptake inhibitor; TCAs=tricyclic antidepressant.
Antidepressants for IBS: Clinical Considerations

- Consider specific symptoms treated
  - TCAs in IBS-D, SSRIs in IBS-C
  - SSRIs/SSRIs for anxiety
- Consider side effect profiles
- SSRIs may be better tolerated than TCAs
- Consider previous use of psychotropic agents

- Start with low dose
- Titrate slowly (every 1-2 weeks)
- Follow up to assess side effects, adherence, and efficacy

**Poor response**
- Switch to different class antidepressant
- Combine treatments as augmentation
- Obtain psychiatry consultation

**Satisfactory response**
- Continue at minimum effective dose for 6 to 12 months
- Long-term therapy may be warranted for some patients

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SNRI=serotonin-norepinephrine reuptake inhibitor.
1. ACG Task Force on IBS. Am J Gastroenterol. 2009;104(suppl 1):S1-S35.

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Efficacy of Internet CBT

- ICBT participants had larger reductions in symptoms, anxiety, and improved quality of life than stress management participants
- More ICBT participants had adequate relief at 6 months than stress management participants

GSRS-IBS=gastrointestinal symptom rating scale—IBS version; ICBT=internet delivered cognitive behavioral therapy
Summary

• There is mounting evidence to support selected lifestyle and dietary recommendations for IBS

• For IBS-D
  • Antibiotics and Probiotics are interesting new options
  • Low dose TCAs can improve pain and diarrhea
  • Alosetron should be considered in pts with severe IBS-D

• For IBS-C
  • Fiber & Laxatives help with constipation symptoms but may not help with pain or global IBS symptoms
  • Lubiprostone & Linaclotide benefit constipation related symptoms, bloating and abdominal pain

Michigan Bowel Control Program
Contact: Donna Sackett, Jen Crawford
877-462-6935

Functional Bowel Disorders Clinic
Contact: GI Scheduling Desk
888-229-7408