Why so irritable?: Treatment Strategies for Irritable Bowel Syndrome

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Pharmacy Grand Rounds
July 25, 2017
Objectives

• Discuss challenges of diagnosing irritable bowel syndrome

• Review non-pharmacologic treatment strategies for the management of irritable bowel syndrome

• Review current and emerging pharmacologic treatment options for irritable bowel syndrome
Assessment Question #1

• Who would be most likely to suffer from IBS?
  A. 16 year old female with migraines
  B. 32 year old female with depression
  C. 45 year old male with obesity
  D. 63 year old female with breast cancer
  E. 78 year old male with diabetes
Irritable Bowel Syndrome

**What is it?**
- Disorder of gut-brain interaction
- Abdominal pain with altered bowel habits
- Alarm features are absent

**Who suffers from it?**
- 12% of North America affected by IBS
- Females > males
- Young adults

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Diagnosing IBS

Rome IV Criteria

Recurrent abdominal pain, on average at least 1 day/week in the past 3 months with ≥ 2 of the following:

- Defecation
- Change in stool frequency
- Change in stool form

IBS Subcategories

- Constipation-predominant
- Diarrhea-predominant
- Mixed

Challenges Diagnosing IBS

- Not associated with radiologic or endoscopic abnormalities
- No reliable biomarkers
- Diagnosis of exclusion, symptom based

IBS: irritable bowel syndrome

Treatment Strategy Considerations

- Presentation
- Severity
- Duration
- Comorbidities
- Current & prior medications

Non-pharmacologic Treatment Options

Diet
Exercise
Behavioral
Education
Dietary Intervention

• Food may trigger symptoms

• Low-FODMAP diet
  • Short-chain, poorly absorbed, highly fermentable carbohydrates
    • Dairy, fruits/vegetables, onions, sorbitol, wheat
  • Most likely to improve bloating & abdominal pain symptoms
  • May reduce symptoms within 1-2 weeks
  • Not intended as a lifetime treatment strategy

• Gluten-free diet?
  • Possible improvement
  • Caution interpretation as wheat contains fructans

FODMAP: Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols

Non-pharmacologic Treatment Strategies

- Cognitive behavioral therapy
  - Improve quality of life
  - Decrease symptom severity

- Regular exercise
  - Walking may reduce symptoms
    - Bloating & gas production
  - Yoga has potential beneficial effects

Pharmacologic Options Based on Subcategory

**IBS-C**
- Fiber
- PEG Laxatives
- Linaclotide
- Lubiprostone

**IBS-D**
- Loperamide
- Alosetron
- Rifaximin
- Eluxadoline
- Ondansetron
- Bile Acid Sequestrants

**IBS**
- TCA
- SSRI
- Anti-spasmodics
- Peppermint Oil
- Probiotics
- STW 5 (Iberogast)
- Antibiotics
- Ginger

**Abbreviations**
- IBS-C: constipation predominant irritable bowel syndrome
- PEG: polyethylene glycol
- IBS-D: diarrhea predominant irritable bowel syndrome
- SSRI: selective serotonin reuptake inhibitor
- IBS: irritable bowel syndrome
- TCA: tricyclic antidepressants
Constipation-predominant IBS

Pharmacologic treatment options
IBS-C Treatment Targets

**Luminal**
- Fiber (diet & supplemental)
- Polyethylene glycol

**Gut**
- Linaclotide
- Lubiprostone

**Brain**
- SSRI

**Adjunctive**
- Exercise
- Hydration

IBS-C: constipation predominant irritable bowel syndrome
SSRI: selective serotonin reuptake inhibitors
Fiber

• Clinical Improvements
  • Global symptom relief
  • Best evidence for use in IBS-C

• Place in Therapy
  • 1st line therapy

• Is there bad fiber?
  • Insoluble fibers → bloating & abdominal discomfort
  • Soluble fibers → preferred

| ACG | Provides overall symptom relief in IBS. Psyllium, but not bran, provides overall symptom relief in IBS. | Rec: weak |
|     |                                                                                                           | QoE: moderate |
| AGA | No recommendation                                                                                       |              |

IBS-C: constipation predominant irritable bowel syndrome
ACG: American College of Gastroenterology
AGA: American Gastroenterological Association

Rec: recommendation
QoE: quality of evidence

Polyethylene Glycol

• Clinical Improvements
  • May improve stool frequency but NOT pain
  • Has shown efficacy for *chronic constipation*

• Place in Therapy
  • Specific symptom relief
  • Adjunctive

<table>
<thead>
<tr>
<th>MOA</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmotic laxative</td>
<td>17 g PO daily</td>
</tr>
</tbody>
</table>

MOA: mechanism of action
PEG: polyethylene glycol
PO: by mouth

ACG: *No evidence that PEG improves overall symptoms & pain in IBS*
Rec: weak
QoE: very low

AGA: *Suggests using laxatives (over no drug treatment) in patients with IBS-C*
Rec: conditional
QoE: low

Linaclotide

- **Clinical Improvements**
  - Global IBS symptoms
  - Complete spontaneous bowel movements
    - Quick effect → within 4 weeks
  - Abdominal pain
    - Gradual effect → within 12 weeks

- **Place in Therapy**
  - Persistent symptoms despite treatment with PEG

<table>
<thead>
<tr>
<th>MOA</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guanylate cyclase-C agonist</td>
<td>290 mcg PO daily</td>
</tr>
</tbody>
</table>

**ACG**
Superior to placebo for the treatment of IBS-C
Rec: strong
QoE: high

**AGA**
Recommends using linaclotide (over no drug treatment) in patients with IBS-C
Rec: strong
QoE: high

Lubiprostone

• Clinical Improvements
  • Constipation

• Place in Therapy
  • Persistent symptoms despite treatment with PEG
  • FDA approved only in women ≥ 18 years of age

<table>
<thead>
<tr>
<th>MOA</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloride channel activator</td>
<td>8 mcg PO BID</td>
</tr>
</tbody>
</table>

**ACG**

*Lubiprostone is superior to placebo for IBS-C*

Rec: strong
QoE: moderate

**AGA**

*Suggests using lubiprostone (over no drug treatment) for IBS-C*

Rec: conditional
QoE: moderate

**Lubiprostone**  
*Drossman, et al.*

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>Two phase-3 double-blind, multisite, RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Lubiprostone 8 mcg BID vs. placebo BID for 12 weeks</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>&gt; 18 yoa with IBS-C</td>
</tr>
<tr>
<td><strong>Outcomes Efficacy</strong></td>
<td></td>
</tr>
</tbody>
</table>
  - Overall responder status (primary)  
  - Monthly responder status (secondary)  
  - Weekly responder rate (secondary)  
  - Symptom rating changes from baseline (secondary) |

### Response Rate

<table>
<thead>
<tr>
<th>Month</th>
<th>Lubiprostone</th>
<th>Placebo</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td>10%</td>
<td>5%</td>
<td>P = 0.078</td>
</tr>
<tr>
<td>Month 2</td>
<td>15%</td>
<td>10%</td>
<td>P = 0.003</td>
</tr>
<tr>
<td>Month 3</td>
<td>20%</td>
<td>15%</td>
<td>P = 0.003</td>
</tr>
<tr>
<td>Overall</td>
<td>25%</td>
<td>20%</td>
<td>P = 0.001</td>
</tr>
</tbody>
</table>

**Notes:**  
RCT: randomized controlled trial  
BID: twice daily  
YOA: years of age  
IBS-C: constipation predominant irritable bowel syndrome

Lubiprostone: Drossman, et al.

• Significant improvement at 3 months vs. placebo:
  • Stool consistency

• Questionable Clinical Improvement?
  • Abdominal pain
  • Constipation severity
  • Straining
  • Quality of life

Linaclotide vs. Lubiprostone Adverse Effects

• **Linaclotide:**
  - Diarrhea (16% - 20%)
    - Usually in 1st week
    - 30% resolve within 7 days
    - Stop all laxative products prior to starting linaclotide
  - Abdominal pain (7%)
  - Flatulence (4% - 6%)

• **Lubiprostone:**
  - Nausea (8% - 29%)
  - Diarrhea (7% - 12%)
  - Abdominal pain (4% - 8%)

Diarrhea-predominant IBS

Pharmacologic treatment options
IBS-D Treatment Targets

Luminal
- Antidiarrheal
- Anticholinergic

Gut
- Rifaximin
- Alosetron
- Eluxadoline
- Ondansetron
- Bile acid sequestrants

Brain
- TCA

TCA: tricyclic antidepressants
Loperamide

• Clinical Improvements
  • Effective antidiarrheal
  • IBS studies failed to show benefit

• Place in Therapy
  • 1st line treatment
    • Low cost
    • Wide availability
    • Minimal adverse effects

<table>
<thead>
<tr>
<th>MOA</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic opioid receptor agonist</td>
<td>4 mg PO then 2 mg after each loose stool (max 16 mg/day)</td>
</tr>
</tbody>
</table>

ACG: Insufficient evidence to recommend loperamide for use in IBS
Rec: strong
QoE: very low

AGA: Suggests using loperamide (over no drug treatment) in patients with IBS-D
Rec: conditional
QoE: very low

Rifaximin

- **Clinical Improvements**
  - Abdominal pain
  - Bloating
  - Global IBS symptoms
  - Stool consistency

- **Place in Therapy**
  - Predominantly studied in middle-aged females
  - Reduced efficacy in males? – conflicting evidence
  - May repeat treatment course up to 2 times

<table>
<thead>
<tr>
<th>MOA</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibits bacterial RNA synthesis</td>
<td>550 mg PO TID x 14 days</td>
</tr>
</tbody>
</table>

**ACG**

- Effective at reducing total IBS symptoms and bloating in IBS-D
  
**AGA**

- Suggests using rifaximin (over no drug therapy) in IBS-D
  
Rec: weak
QoE: moderate

Rec: conditional
QoE: moderate

Bile Acid Sequestrants

• Clinical Improvements:
  • Diarrhea

• Place in Therapy:
  • IBS-D with bile acid malabsorption
    • 1/3 of IBS-D patients have bile acid malabsorption
  • Diagnostic testing possible – but not widely available

<table>
<thead>
<tr>
<th>MOA</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binds bile acid to prevent reabsorption</td>
<td>Agent specific</td>
</tr>
</tbody>
</table>

Eluxadoline

- Clinical Improvements
  - Abdominal pain
  - Global symptoms
  - Quality of life

- Place in Therapy
  - Persistent symptoms despite treatment

<table>
<thead>
<tr>
<th>MOA</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mu- &amp; kappa-opioid receptor agonist</td>
<td>• 75 mg PO BID</td>
</tr>
<tr>
<td>• Delta-opioid receptor antagonist</td>
<td>• 100 mg PO BID</td>
</tr>
</tbody>
</table>

Eluxadoline

**Design**
2 randomized, double-blind, placebo-controlled, parallel group, multicenter studies

**Intervention**
Eluxadoline 75 mg, 100 mg, or placebo BID

**Population**
2428 patients, 18 – 80 years of age with IBS-D

**Outcome – Efficacy**
- Proportion of patients who had a composite response

---

**Weeks 1 – 12 Composite Response**

<table>
<thead>
<tr>
<th>Group</th>
<th>Response</th>
<th>75 mg</th>
<th>Placebo</th>
<th>100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS-3001</td>
<td>P = 0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBS-3002</td>
<td>P &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled Data</td>
<td>P &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


BID: twice daily
Eluxadoline

• Adverse Events:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo</th>
<th>Eluxadoline 75 mg</th>
<th>Eluxadoline 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>2.5%</td>
<td>7.4%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>5.1%</td>
<td>8.1%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>4.1%</td>
<td>5.8%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0</td>
<td>0.2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Sphincter of Oddi spasms</td>
<td>0</td>
<td>0.1%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

• FDA Warning: avoid in patients without a gallbladder
• Discontinue therapy if severe constipation for > 4 days

Alosetron

• Clinical Improvements
  • Abdominal symptoms
  • Diarrhea
  • Global symptoms

• Place in Therapy
  • FDA approved only in females
  • Women + severe symptoms + failed conventional therapy

• REMS: ischemic colitis & serious complications of constipation

<table>
<thead>
<tr>
<th>MOA</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective 5-HT3 antagonist</td>
<td>0.5 mg PO BID</td>
</tr>
</tbody>
</table>

ACG  | Effective in females with IBS-D | Rec: weak  
     | QoE: moderate                  |

AGA  | Suggests using alosetron (over no drug treatment) in patients with IBS-D to improve global symptoms | Rec: conditional  
     | QoE: moderate                  |


BID: twice daily  
REMS: risk evaluation and mitigation strategies
Ondansetron

- Clinical Improvements
  - Stool consistency
  - Global IBS symptoms
  - Urgency
  - Stool frequency
  - Bloating

- Place in Therapy
  - May be useful in IBS-D
  - Less potent than alosetron
  - Easier to prescribe than alosetron

<table>
<thead>
<tr>
<th>MOA</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective 5-HT3 antagonist</td>
<td>4 mg TID</td>
</tr>
</tbody>
</table>

IBS

Pharmacologic Treatment Options
Antispasmodics: hyoscyamine, dicyclomine

- Clinical Improvements
  - Global symptoms
  - Cramping
- Place in Therapy
  - Post-prandial IBS symptoms
- Limitations To Use:
  - Adverse effects → dry mouth, dizziness, blurred vision

<table>
<thead>
<tr>
<th>ACG</th>
<th>Certain antispasmodics* provide symptomatic short-term relief in IBS. Adverse events are more common with antispasmodics than placebo.</th>
<th>Rec: weak QoE: low</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA</td>
<td>Suggests using antispasmodics (over no drug treatment) in patients with IBS</td>
<td>Rec: conditional QoE: low quality</td>
</tr>
</tbody>
</table>

*otilonium, hyoscine, cimetropium, pinaverium, dicyclomine

ACG

AGA

Probiotics – not created equal

• Specific probiotics with **supportive evidence** for overall symptoms & abdominal pain:
  • *Bifidobacterium bifidum* MIMBb75
  • *B. longum* subsp. *infantis* 35624
  • *Escherichia coli* DSM17252

• Favorable safety profile in IBS
Probiotics

**High**
Supportive evidence for benefit (*should*)
- Overall IBS symptoms
- Abdominal pain

**Very Low**
No evidence to support use
- Flatus in IBS
- Diarrhea in IBS

| ACG | Taken as a whole, probiotics improve global symptoms, bloating, and flatulence in IBS | Rec: weak | QoE: low |
| AGA | No recommendations |

Antidepressants

**TCA**
- Use in IBS-D
  - Global symptoms
  - Pain
- Dose: start low (10 – 25 mg) at bedtime
  - Titrate according to symptom response & tolerability

**SSRI**
- Use in IBS-C
  - Global symptoms
  - Pain
- Dose: start lower end of standard dosing

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**ACG**
*Effective in symptom relief in IBS.*
*Side effects are common and may limit patient tolerance*

**AGA**
*Suggests using TCAs (over no drug treatment) in patients with IBS*
*Suggests against using SSRIs for patients with IBS*

Rec: weak
QoE: high

Rec: conditional
QoE: low

---

TCA: tricyclic antidepressants
SSRI: selective serotonin reuptake inhibitors

Herbals

- **Peppermint oil**
  - Dose: 0.2 – 0.4 mL (187 – 500 mg) TID
  - Try enteric-coated formulation to ↑ efficacy & ↓ heartburn
  - Superior to placebo in improving IBS symptoms. The risk of adverse events is no greater with peppermint oil than with placebo
    - ACG: Rec: weak
    - AGA: No recommendation

- **STW 5 (Iberogast®)**
  - Dose: 20 drops in ½ glass water TID
  - Reduces global symptoms & abdominal pain

- **Ginger**
  - 1 – 2 gm/day not as effective as placebo


TID: three times daily
Peppermint Oil: Khanna, et al.

<table>
<thead>
<tr>
<th>Design</th>
<th>Systematic review &amp; meta-analysis of randomized, placebo-controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Peppermint oil versus placebo, treated for 2 – 12 weeks</td>
</tr>
<tr>
<td>Population</td>
<td>9 studies, ( n = 47 – 178 ) patients per study</td>
</tr>
<tr>
<td>Outcome – Efficacy</td>
<td>• Proportion of patients with global improvement of IBS symptoms • Proportion of patients with improvement in abdominal pain</td>
</tr>
</tbody>
</table>

- Improvement of global symptoms: Peppermint Oil vs. Placebo, \( P < 0.00001 \)
- Improvement of abdominal pain: Peppermint Oil vs. Placebo, \( P < 0.00001 \)
- Adverse Event: Peppermint Oil vs. Placebo

Emerging IBS Therapies

Pharmacologic Treatment Options
Antibiotics?

• Growing & controversial literature → neomycin & metronidazole

• Emerging role
  • IBS-D
  • IBS with small intestinal bacterial overgrowth

• Risk factors for small intestinal bacterial overgrowth:
  • Achlorhydria: gastrectomy, advancing age, PPIs
  • Intestinal dysmotility
  • Anatomic alterations
  • Crohn’s disease
  • Celiac disease

• How are antibiotics beneficial?
  • Altering gut flora
  • Reduce the overall number of colonic bacteria
    • Reduce intestinal gas

PPI: proton pump inhibitor
Pharmacologic Options Based on Symptoms

**Stomach Pain**
- Alosetron
- Anti-spasmodics
- Eluxadoline
- Linaclotide
- Lubiprostone

**Constipation**
- Fiber
- Linaclotide
- Lubiprostone
- PEG Laxatives

**Diarrhea**
- Alosetron
- Bile acid sequestrant
- Eluxadoline
- Loperamide
- Ondansetron
- Rifaximin

**Bloating**
- Probiotics
- Rifaximin


PEG: polyethylene glycol
Sally is a 37 year old female who was just diagnosed with IBS-C. She would like your recommendation on the best way to start managing her abdominal pain & bloating.
Assessment Question #2

A. Start eating wheat bran
B. Start ginger 550 mg once daily
C. Eliminate specific carbohydrates from her diet
D. Start a probiotic containing lactobacillus
Assessment Question #3

Unfortunately, due to persistent symptoms Sally recently started linaclotide 290 mcg daily for her IBS-C. After 1 week of therapy she does not notice significant symptom improvement and is wondering what to do next. What advice would you give Sally?
Assessment Question #3

A. Start polyethylene glycol for symptom relief
B. Stop linaclotide & try lubiprostone
C. Continue linaclotide for 1 more week, if no response then stop
D. Continue linaclotide for at least 4 weeks
Summary

• Diagnosis of exclusion
• Holistic treatment approach
• Target medications based on symptoms
Questions & Discussion

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