Treatment of Irritable Bowel Syndrome: What works and what doesn’t!

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Prevalence of IBS
What is IBS?

<table>
<thead>
<tr>
<th>Manning</th>
<th>Rome I</th>
<th>Rome II</th>
<th>Rome III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain relieved by defecation</td>
<td>&gt;12 wk of continuous or recurrent symptoms of abdominal pain or discomfort:</td>
<td>&gt;12 wk, which need not be consecutive, in the preceding 12 mo, of abdominal discomfort or pain that has 2 or more of 3 features:</td>
<td>Recurrent abdominal pain or discomfort at least 3 d/mo for past 3 mo, with symptom onset &gt;6 mo before diagnosis, associated with 2 or more of the following:</td>
</tr>
<tr>
<td>Looser stools with the onset of pain</td>
<td>1. Relieved with defecation or 2. Associated with change in frequency of stool or 3. Associated with a change in consistency of stool</td>
<td>Relieved with defecation  Onset associated with change in stool frequency  Onset associated with a change in form (appearance) of stool</td>
<td>Improvement with defecation  Onset associated with a change in frequency of stool  Onset associated with a change in stool form (appearance)</td>
</tr>
<tr>
<td>More frequent stools with the onset of pain</td>
<td>Two or more of the following, at least on one-fourth of occasions or days: 1. Altered stool frequency 2. Altered stool form 3. Passage of mucus 4. Bloating or feeling of abdominal distention</td>
<td></td>
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</tbody>
</table>
What is IBS?

Rome III criteria for diagnosis of IBS:
• Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with two 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
• With symptom onset at least 6 months prior to diagnosis.

Drossman DA. 2006
What is IBS?

**IBS with constipation (IBS-C)**
- hard or lumpy stools at least 25 percent of the time
- loose or watery stools less than 25 percent of the time

**IBS with diarrhea (IBS-D)**
- loose or watery stools at least 25 percent of the time
- hard or lumpy stools less than 25 percent of the time

**Mixed IBS (IBS-M)**
- hard or lumpy stools at least 25 percent of the time
- loose or watery stools at least 25 percent of the time

**Unsubtyped IBS (IBS-U)**
- hard or lumpy stools less than 25 percent of the time
- loose or watery stools less than 25 percent of the time
Physiopathology of IBS

Triggers and Predisposing Factors

Environmental factors
- Central:
  - Psychological stress
  - Anxiety/Depression
- Peripheral:
  - Gastroenteritis
  - Diet
  - Medications
  - Life habits

Host factors
- Genetics
- Disease conditions

Altered intestinal function
- Sensory-motor function
- Barrier function

Altered intestinal microbiota
- Composition
- Function

Altered intestinal immune system
- Mast cell activation
- Inflammatory cytokines

CNS

HPA ANS

ENS

Functional GI symptoms
Physiopathology of IBS
Treatment

- Multidisciplinary approach
- Referral to a pain treatment centre
  - +
- Pharmacotherapy
- Psychological treatments
  - +
- Education
- Reassurance
- Dietary modification

- Severe
- Moderate
- Mild
Education

• A limited diagnostic strategy is non-inferior to a strategy of exclusion for patients with IBS
  (Begtrup LM et al. Clin Gastroenterol Hepatol 2013)

• No association between a negative colonoscopy and reassurance or improved HRQOL in IBS patients aged <50 years
  (Spiegel B et al. Gastrointest Endosc 2005)

  Most IBS patients will not benefit from more investigations
Education

Education and reassurance are essential elements of clinical management

Patients need:

• Answering questions and listening
• Information about the nature of their condition and where to obtain more information
• Explanation of the treatment plan

Halpert A et al, Dig Dis Sci 2010
Diet

60% of patients

• Believe that their symptoms are triggered by certain food items

• Had either limited or excluded certain food items from their daily diet

Diet/Fiber

- 14 RCTs involving 906 patients
- Significant benefit of fiber (RR= 0.86, NNT=10)
- The benefit was only for soluble fiber (RR= 0.83, NNT= 7)
- No effect seen with bran (RR=0.9)

Diet/Fiber

Proportion of patients with adequate relief of symptoms each week. R <0.05

- Certain forms of fiber, particularly Bran, can exacerbate abdominal bloating/distension

Bijkerk CJ. Et al. BMJ 2009
Diet/Lactose and fructose

Prevalence of lactose and fructose intolerance in IBS patients

Adequate global symptom relief: 50 to 80% of patients

(Wilder-Smith CH et al. Aliment Pharmacol Ther 2013)
Low FODMAPs diet induce changes:

- Gastrointestinal endocrine cells (Mazzawi T et al. Eur Clin Nutr 2015)
Diet/FODMAP

Traditional IBS diet:
- Small frequent meals
- Peel and divide foods
- Chew thoroughly
- Boil food
- Reduce fatty, spicy foods, onions, coffee and alcohol
- Avoid carbonated beverages and sweeteners that end with -ol
- Distribute fiber

Bohn I et al. Gastroenterol 2015
Diet/Gluten

Putative mechanisms of clinical benefits observed with GFD:

• Gluten itself
• Other wheat proteins
• Highly fermentable short chain carbohydrates
Diet/Gluten

RCT in IBS-D
NCGS (Vazquez-Roque et al. Gastroenterol 2013)

- GCD was associated with higher small bowel permeability
- Small bowel permeability was greater in HLA DQ2/8 +
Diet/Gluten

Placebo-controlled, crossover study of patients with IBS-like symptoms on subjects believed to have NCGS:

• Gastrointestinal symptoms significantly improved when consuming a low FODMAPs diet
• Symptoms were not worsened by either a low- or high-dose challenge with gluten.
• Carbohydrate content of wheat rather than gluten is responsible for triggering NCGS symptoms

Biesiekierski JR et al. Gastroenterology 2013
Probiotics

Role of gut microbiota in IBS

• Differences between microbiota in IBS and non-IBS population

• Development of IBS after intestinal infection

• Preliminary data on FMT

• Efficacy of certain probiotics in the treatment of IBS
Probiotics

• Why is the evidence still poor?
  1. Heterogeneity of the studies questions the value of meta-analyses
  2. Use of different bacterial strains
  3. Use of different mixture of these strains
  4. Use of different dosages
• Probiotics may improve symptoms of IBS (limited evidence) and can be used as supplement to standard therapy
Non pharmacologic and pharmacologic treatment
Psychological treatments

• IBS shares many features with other syndromes such as fibromyalgia, chronic fatigue syndrome, somatoform disorders, and unexplained urological conditions

• “Functional pain syndromes”
Psychological treatments

- Patients who are distressed by their symptoms
- Open to the idea that psychological factors play some role and are willing to participate in this approach
- History of sexual abuse
Psychological treatments

- Practical option for patients who fail standard medical therapy
- OR
- Introduce together with pharmacotherapy
- OR
- Use just in specific subgroup
Alternative therapies

• Acupuncture targeting serotonergic, cholinergic, and glutamatergic pathways:
  Increase the concentration of endogenous opioids
  Reduces visceral and global pain perception
• Combination of TCM and western medication?
Pharmacologic treatment/IBS-D

Loperamide:

- Synthetic peripheral µ-opioid receptor agonist, decreases colon transit and increases water absorption
- Double-blind, placebo-controlled trials of patients with IBS-D, loperamide significantly improved stool consistency
Pharmacologic treatment/IBS-D

Antispasmodics:
- Anticholinergic: Systematic review of randomized controlled trials: Reduction of IBS symptoms

- Peppermint oil (antispasmodic that exerts its effects by reducing the influx of calcium in smooth muscle cells): Meta-analysis found peppermint oil to be significantly superior to placebo for global improvement of IBS symptoms and improvement in abdominal pain
Pharmacologic treatment/IBS-D

5-HT3 Receptor Antagonists:

- **Alosetron** reduced abdominal pain and discomfort, stool frequency and urgency in women with IBS-D.
  
  Camilleri M et al. Lancet 2000

- Removed from the market in 2000 following reports of constipation (25%) and ischemic colitis (0.1%)
Pharmacologic treatment/IBS-D

5-HT3 Receptor Antagonists:
• Ondansetron: (Garsed et al. Gut 2014)
Significantly more effective than placebo as assessed by improvements in
• Urgency ($P<.001$)
• Frequency ($P<.001$)
• Bloating ($P=.002$)
• Symptom severity ($P=.001$)
Pharmacologic treatment/IBS-D

Rifaximin:
• IBS non C, TARGET 1 and 2 (550 mgTID)
• Outcomes included improvement in:
  - Bloating
  - Abdominal pain
  - Stool consistency

Pharmacologic treatment / IBS-D

Mesalazine:

• RCT for 12 weeks, 180 unselected IBS:
  Primary endpoint = satisfactory relief of abdominal pain was no different from placebo
  Barbara et al. Gut 2015

• 12 weeks, 136 IBS-D:
  Primary endpoint = average stool frequency for weeks 11 and 12 not different from placebo
  Lam et al. Gut 2015
Pharmacologic treatment/IBS-D

Eluxadoline:
Mixed µ-opioid receptor agonist and δ-opioid receptor antagonist
Improves urgency and stool consistency for at least 50% of the days during weeks 1 through 12 of treatment (P<0.005)
Less effect on abdominal pain
Acute pancreatitis is reported

Lembo A et al. DDW 2014
## Pharmacologic treatment for IBS-C

<table>
<thead>
<tr>
<th>Pharmacologic agent</th>
<th>Quality of evidence for IBS-C</th>
<th>Quality of evidence for CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laxatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psyllium</td>
<td>No RCTs</td>
<td>Moderate</td>
</tr>
<tr>
<td>Docusate sodium</td>
<td>No RCTs</td>
<td>Low</td>
</tr>
<tr>
<td>Lactulose</td>
<td>No RCTs</td>
<td>Moderate</td>
</tr>
<tr>
<td>PEG</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Senna</td>
<td>No RCTs</td>
<td>Low</td>
</tr>
<tr>
<td>Bisacodyl</td>
<td>No RCTs</td>
<td>Moderate</td>
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<tr>
<td>Prokinetics</td>
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<tr>
<td>Prucalopride</td>
<td>No RCTs</td>
<td>High</td>
</tr>
<tr>
<td>Naropride</td>
<td>No RCTs</td>
<td>Low</td>
</tr>
<tr>
<td>Velusetrag</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Rose-010</td>
<td>Moderate</td>
<td>No RCTs</td>
</tr>
<tr>
<td>Secretagogues</td>
<td></td>
<td></td>
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<tr>
<td>Linaclotide</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Plecanatide</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Bile acid modulators</td>
<td></td>
<td></td>
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<tr>
<td>CDC</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Elobixibat</td>
<td>No RCTs</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Pharmacologic treatment/IBS-C

• Bulking agents: Ispaghula
  20% improvement versus Placebo. Benefits include:
  1. Bowel softening
  2. Acceleration of transit
  3. Reduction in days without bowel movement
  Prior et al. Gut 1987

• PEG : > BM
  Similar to placebo after 4 weeks (Pain, abd discomfort)
  Chapman RW et al. Am J Gastroenterol 2013
Pharmacologic treatment/IBS-C

- Prosecretory agents
Pharmacologic treatment/IBS-C

Lubiprostone:
- Chloride channel type 2 activator
- Continued improvement in overall response, for up to 13 months
- Women with IBS-C at a dose of 8 µg twice daily

Drossman et al. Aliment Pharmacol Ther 2009
Pharmacologic treatment/IBS-C

Linaclotide:
- Acts on the guanylate cycloase C receptor
- Approved for men and women with IBS-C at a dose of 290 µg once daily.

Pharmacologic treatment/IBS-C

Plecanatide (SP-304): Mechanism-of-Action
Activation of Cl⁻ Channels promotes Fluid Secretion into Lumen

Lumen
- CIC2
- CFTR
- Plecanatide/Linaclotide

Serosa
- AMITIZA®
- PKA
- PKG II
- cGMP
- PDE III
- Anti-proliferative
- Anti-inflammatory
- Downregulation of cytokines

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Pharmacologic treatment/IBS-C

Elobixibat:
• A minimally absorbed ileal bile acid transporter inhibitor.
• Increase spontaneous bowel movements. IBS-C?

Chey WD et al. Am J Gastroenterol 2011

Tenapanor:
• Na reuptake inhibitor
• Increase complete spontaneous bowel movements (phase 2b clinical trial, SBM 60.7% with tenapanor vs 33.7% with placebo \(P<.001\))
Centrally acting treatment

1. Psychiatric co-morbidity
2. Effects on pain processing and modulation
3. Effects on psychological distress associated with IBS
4. Non specific effects on general well-being
Centrally acting treatment

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Proposed antidepressant mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs Tertiary amine</td>
<td>Amitriptyline</td>
<td>NE and 5-HT reuptake inhibition</td>
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<tr>
<td></td>
<td>Imipramine</td>
<td>NE and 5-HT reuptake inhibition</td>
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<tr>
<td></td>
<td>Doxepin</td>
<td>NE and 5-HT reuptake inhibition</td>
</tr>
<tr>
<td></td>
<td>Trimipramine</td>
<td>NE and 5-HT reuptake inhibition</td>
</tr>
<tr>
<td></td>
<td>Clomipramine</td>
<td>Mixed action</td>
</tr>
<tr>
<td>Secondary amine</td>
<td>Nortriptyline</td>
<td>NE reuptake inhibition</td>
</tr>
<tr>
<td></td>
<td>Desipramine</td>
<td>NE reuptake inhibition</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Citalopram</td>
<td>5-HT reuptake inhibition</td>
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<tr>
<td></td>
<td>Escitalopram</td>
<td>5-HT reuptake inhibition</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>5-HT reuptake inhibition</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>5-HT reuptake inhibition</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>5-HT reuptake inhibition</td>
</tr>
<tr>
<td>Other newer</td>
<td>Bupropion</td>
<td>Dopamine reuptake inhibition</td>
</tr>
<tr>
<td>antidepressants</td>
<td>Duloxetine</td>
<td>NE and 5-HT reuptake inhibition</td>
</tr>
<tr>
<td></td>
<td>Nefazodone</td>
<td>Pre- and postsynaptic activity</td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
<td>Pre- and postsynaptic activity</td>
</tr>
<tr>
<td></td>
<td>Trazodone</td>
<td>Mixed action</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>NE and 5-HT reuptake inhibition</td>
</tr>
</tbody>
</table>
Centrally acting treatment

Antidepressants: classes

- TCA
  - tricyclic antidepressants
    - amitriptyline
    - doxepine
    - desipramine
    - nortriptyline (NRI)

- selective serotonin reuptake inhibitors
  - fluoxetine
  - paroxetine
  - sertraline
  - (es)citalopram

- serotonin noradrenalin reuptake inhibitors
  - venlafaxine
  - duloxetine

- NaSSA
  - noradrenergic and specific serotonergic antidepressant
    - mirtazapine
Centrally acting treatment

- Significant effect of antidepressants in IBS on overall improvement, OR= 2.6 (CI 1.9-3.5).

- Analysis restricted to higher quality studies, OR= 1.9 (CI 1.3-2.7) in favour of antidepressants

Clouse RE et al. Gut 2005
Centrally acting treatment

Dose to be titrated based on response and psychiatric co-morbidity
Conclusion

IBS patient

“This is not cancer or colitis”

I will try to get ride of him with some safe (probably ineffective) treatment
Conclusion

OR

I will try to help by identifying:

1. Physiological basis of his symptoms
2. Psycho-social state
3. Most proven efficacious treatment that will be accepted