Current and Emerging Pharmacological Treatments in Irritable Bowel Syndrome

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Harvard Medical School
What is the general approach to treatment?
General Treatment Approach to Patients with IBS: Mild Symptoms

- Diet, lifestyle advice
- Positive diagnosis
- Explain, reassure
**General Treatment Approach to Patients with IBS: Mild Symptoms**

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

- **Moderate**
  - Follow-up visit
  - Manage stress
  - Pharmacotherapy

+ Diet, lifestyle advice
+ Positive diagnosis
+ Explain, reassure
General Treatment Approach to Patients with IBS: Mild Symptoms

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

Moderate

- Multidisciplinary approach
- Psychological treatments
- Improve functioning
- Follow-up visit
- Manage stress
- Pharmacotherapy

Severe

Mild

- Diet, lifestyle advice
- Positive diagnosis
- Explain, reassure
Pharmacologic Treatment Options in IBS

**Abdominal pain /discomfort**
- Antispasmodics
- Antidepressants
  - TCAs / SSRIs
- Alosetron

**Altered bowel function**
- Fiber
- Osmotic laxatives
- Tegaserod (withdrawn from US in 4/08)
- Lubiprostone

**Bloating**
- Probiotics
- Antibiotics
- Tegaserod

**Bloating /distension**
- Antispasmodics
- Antidepressants
  - TCAs / SSRIs
- Alosetron

**Diarrhea**
- Antidiarrheals
  - Loperamide
  - Diphenoxylate
- Alosetron

**Constipation**
- Fiber
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*Brandt LJ et al. Am J Gastroenterology 2002; 97(11 Suppl.):S7
Drossman DA et al. Gastroenterology 2002; 123:2108
Saad R, Chey WD. Expert Opinion Invest Drugs 2008;17:117*
### ACG Task Force: Management of IBS-C: Grading recommendations

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Methodological quality of supporting evidence and Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A: Strong recommendation; high quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies. Can apply to most patients in most circumstances</td>
</tr>
<tr>
<td>1B: Strong recommendation; moderate quality evidence</td>
<td>RCTs with important limitations (inconsistent results/ methodology) or exceptionally strong evidence from observational studies. Can apply to most patients in most circumstances</td>
</tr>
<tr>
<td>1C: Strong recommendation; low or very-low quality evidence</td>
<td>Observational studies or case series. Can apply to most patients in most circumstances</td>
</tr>
</tbody>
</table>

*ACG IBS Task Force, Am J Gastro 2009; 104 (S1): S1-S35*
## ACG Task Force: Management of IBS-C: Grading recommendations

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<tr>
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<tbody>
<tr>
<td>2A: Weak recommendation; high quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies. Best action may differ depending on circumstances / patient</td>
</tr>
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<td>2B: Weak recommendation; moderate quality evidence</td>
<td>RCTs with important limitations (inconsistent results/ methodology) or exceptionally strong evidence from observational studies. Best action may differ depending on circumstances / patient</td>
</tr>
<tr>
<td>2C: Weak recommendation; low or very-low quality evidence</td>
<td>Observational studies or case series. Other alternatives may be equally reasonable.</td>
</tr>
</tbody>
</table>
What are the therapies for IBS with constipation?
Pharmacologic Treatment Options in IBS

Bloating
- Probiotics
- Antibiotics
- Tegaserod

Abdominal pain/pain/discomfort
- Antispasmodics
- Antidepressants
  - TCAs / SSRIs
- Alosetron

Altered bowel function

Diarrhea
- Antidiarrheals
  - Loperamide
  - Diphenoxylate
- Alosetron

Constipation
- Fiber
- Osmotic laxatives
- Tegaserod (withdrawn from US in 4/08)
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Abdominal pain /discomfort

Brandt LJ et al. Am J Gastroenterology 2002; 97(11 Suppl.):S7
Drossman DA et al. Gastroenterology 2002; 123:2108
Saad R, Chey WD. Expert Opinion Invest Drugs 2008;17:117
Efficacy of Fiber in IBS-C

- 13 randomized clinical trials
  - Wheat bran, corn fiber, calcium polycarbophil, and psyllium
  - Low-intermediate quality studies with small sample sizes
  - Psyllium (4/5 studies) improved global IBS symptoms and ease of stool passage but not pain.

- Side effects: may increase intestinal gas, bloating and abdominal discomfort

- Appropriate for constipation-predominant symptoms

Brandt LJ et al. Am J Gastroenterol 2002;97 suppl:S7-26
Laxatives in IBS-C

• Are generally effective at improving bowel frequency and consistency in chronic constipation
• However there is almost no data in IBS-C
  – Only one small study with polyethylene glycol (PEG) in IBS-C
### ACG Task Force: Management of IBS-C: Dietary fiber, bulking agents, laxatives

<table>
<thead>
<tr>
<th>Agents</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psyllium hydrophilic muciloid (ispaghula husk): <em>moderately effective</em></td>
<td>Grade 2C</td>
</tr>
<tr>
<td>Wheat bran: <em>no more effective than placebo in relief of global IBS symptoms, cannot be recommended for routine use</em></td>
<td>Grade 2C</td>
</tr>
<tr>
<td>Polyethylene glycol (PEG): <em>improved stool frequency but not abdominal pain in one small study in IBS-C</em></td>
<td>Grade 2C</td>
</tr>
</tbody>
</table>
Tegaserod produced a significantly greater response rate than placebo.

Kellow J et al. Gut 2003; 52:671*
Tegaserod

- Are Suspended from the US market – March 30, 2007
  - Increased incidence of CV events and CVAs between those randomized to tegaserod vs. placebo in clinical trials

<table>
<thead>
<tr>
<th># Events</th>
<th>Total patients</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegaserod</td>
<td>13</td>
<td>11,614</td>
</tr>
<tr>
<td>Placebo</td>
<td>1</td>
<td>7,031</td>
</tr>
</tbody>
</table>

- Restricted use program – July 2007
  - For women aged < 55 with CC or IBS-C

P=0.02; 3 MIs, one sudden cardiac death, 6 unstable angina, 3 CVAs (blinded, adjudicated data)
Tegaserod pts who developed events had a history of cardiac disease or risk factors.

Lubiprostone:
A chloride channel activator

• FDA approved in 4/08 for women with IBS-C

• Locally-acting gastrointestinal-targeted bicyclic functional fatty acid
  – rapidly and extensively metabolized in the stomach and jejunum

• Selectively activates type II chloride channels enhancing intestinal fluid secretion

• Also indicated for:
  – treatment of chronic idiopathic constipation in the adult population

FDA Consum 2006; 40: 8
Lubiprostone for IBS-C: Data from 2 Phase III Trials

- 12-week treatment period
- 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
- Most common SE was nausea (8%)

Overall Responders

<table>
<thead>
<tr>
<th>Lubiprostone 8 mcg bid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.9</td>
<td>10.1</td>
</tr>
<tr>
<td>* P=0.001</td>
<td></td>
</tr>
</tbody>
</table>

Drossman DA et al. Gastroenterology 2007; 132:639f
<table>
<thead>
<tr>
<th>Agents</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubiprostone 8µg bid: is more effective than placebo in relieving global IBS symptoms in women with IBS-C</td>
<td>Grade 1B</td>
</tr>
</tbody>
</table>
What are the therapies for IBS with pain?
Pharmacologic Treatment Options in IBS

- **Abdominal pain /discomfort**
  - Antispasmodics
  - Antidepressants
    - TCAs / SSRIs
  - Alosetron

- **Bloating /distension**
  - Probiotics
  - Antibiotics
  - Tegaserod

- **Altered bowel function**
  - Fiber
  - Osmotic laxatives
  - Tegaserod (withdrawn from US in 4/08)
  - Lubiprostone

- **Diarrhea**
  - Antidiarrheals
    - Loperamide
    - Diphenoxylate
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- **Constipation**
  - Fiber
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References:
- Brandt LJ et al. Am J Gastroenterology 2002; 97(11 Suppl.):S7
- Drossman DA et al. Gastroenterology 2002; 123:2108
- Saad R, Chey WD. Expert Opinion Invest Drugs 2008;17:117
Antispasmodics in IBS

- Meta-analysis of 24 RCTs
  - Octylonium was effective in relieving global IBS symptoms
  - Heterogeneity of trials, and small sample sizes
- 3 RCTs using Hyoscine
  - More likely to decrease IBS Symptoms vs Placebo
    \( RR=0.63 \ (95\% \ CI=0.51-0.78) \)
- 4 RCTs using peppermint oil
  - More likely to decrease IBS symptoms
    \( RR =0.42 \ (CI = 0.32-0.59) \)
- Side effects: dry mouth, constipation, urinary retention and visual disturbances

# ACG Task Force: Management of IBS-C: Antispasmodics

<table>
<thead>
<tr>
<th>Agents</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Antispasmodics</strong></td>
<td>-</td>
</tr>
<tr>
<td>Hyoscine, cimetropium, pinaverium: provide short-term relief of abdominal pain/discomfort in IBS; evidence for safety and tolerability is limited</td>
<td>Grade 2C</td>
</tr>
<tr>
<td>Peppermint oil: superior to placebo in IBS in a small number of studies</td>
<td>Grade 2B</td>
</tr>
</tbody>
</table>
Antidepressants in IBS

- 6 placebo controlled RCTs with tricyclic antidepressants
- Trends favoring TCAs but only one trial showed statistically significant benefit
- In meta-analysis, TCAs were associated with a decrease in IBS symptoms vs placebo (RR=0.77; CI 0.66-0.9)
Tricyclics Antidepressants in IBS

- Moderate to Severe FGIDs (n=201)
- RDBPC with desipramine
- ITT Analysis: 60% vs 47%; p=0.13
- PP Analysis (n=153) 73% vs 49% p=0.006 (NNT = 4)
- 26% of patients d/c desipramine secondary to SEs (e.g., constipation, fatigue)

Drossman Gastro 2003; 125:19
SSRIs in IBS

- Limited number of studies in IBS
  - (fluoxetine, n=2; paroxetine, n=1; citalopram, n=1)
- Improvement in overall well-being, however
  - no studies show benefit in bowel habits
  - Improvement is seen in some, but not all, studies on abdominal pain
- Safety and tolerability in IBS has not been well assessed
- Further studies needed to clarify the role of SSRIs in treatment of IBS.

Vahedi et al, Aliment Pharmacol Ther 2005; 22: 381
### ACG Task Force: Management of IBS-C: Antidepressants (TCAs & SSRIs)

<table>
<thead>
<tr>
<th>Agents</th>
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</tr>
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<tbody>
<tr>
<td>TCAs: more effective than placebo at relieving global IBS symptoms and appear to reduce abdominal pain. There is limited data on safety and tolerability in IBS</td>
<td>Grade 1B</td>
</tr>
<tr>
<td>SSRIs: more effective than placebo at relieving global IBS symptoms and appear to reduce abdominal pain. There is limited data on safety and tolerability in IBS</td>
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*ACG IBS Task Force, Am J Gastro 2009; 104 (S1): S1-S35*
What are the therapies for IBS with bloating?
Pharmacologic Treatment Options in IBS

**Bloating**
- Probiotics
- Antibiotics
- Tegaserod

**Abdominal pain /discomfort**
- Antispasmodics
- Antidepressants
  - TCAs / SSRIs
- Alosetron

**Bloating / distension**

**Altered bowel function**

**Diarrhea**
- Antidiarrheals
  - Loperamide
  - Diphenoxylate
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**Constipation**
- Fiber
- Osmotic laxatives
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**Brandt LJ et al. Am J Gastroenterology 2002; 97(11 Suppl.):S7**
**Drossman DA et al. Gastroenterology 2002; 123:2108**
**Saad R, Chey WD. Expert Opinion Invest Drugs 2008;17:117**
Probiotics in IBS

- Over 19 RCTs studies in IBS using a variety of species, strains and doses of probiotics

- Lactobacilli do not appear to have an effect on IBS symptoms

- Bifidobacteria species and certain combinations of probiotics demonstrate some efficacy

- Grade 2C
**Bifidobacter infantis** alleviates IBS symptoms and normalizes pro-inflammatory cytokines

- Significantly less difficult BMs with *B. infantis* vs placebo
- PBMC cytokine levels similar to controls with *B. infantis*
- No effect on stool passage
- Currently generalizations about benefits of probiotics in IBS cannot be made

*N=77; *p<0.05*

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**O’Mahony et al, Gastroenterology 2005; 128: 541–51**
**Bifidobacterium infantis** in Women with IBS:

Improvements in abdominal pain, bloating, bowel dysfunction were seen.

Whorwell PJ et al. J Gastroenterol 2006; 101:1581
# Antibiotic therapy in IBS

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Intervention</th>
<th>Control</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nayak et al</td>
<td>45</td>
<td>Metronidazole 1.2 g</td>
<td>Placebo</td>
<td>10 days</td>
<td>Significant reduction in global symptom score</td>
</tr>
<tr>
<td>Pimentel et al</td>
<td>111</td>
<td>Neomycin</td>
<td>Placebo</td>
<td>10 days</td>
<td>Reduction in global symptom score 35% vs 11%</td>
</tr>
<tr>
<td>Sharara et al</td>
<td>124</td>
<td>Rifaximin 800 mg</td>
<td>Placebo</td>
<td>10 days</td>
<td>Reduction in global symptom score 40% vs 18%</td>
</tr>
<tr>
<td>Pimentel et al</td>
<td>87</td>
<td>Rifaximin 1.2 g</td>
<td>Placebo</td>
<td>10 days</td>
<td>Reduction in global symptom score 36% vs 21%</td>
</tr>
<tr>
<td>Scarpellini et al</td>
<td>80</td>
<td>Rifaximin 1.6 g</td>
<td>Rifaximin 1.2 g</td>
<td>7 days</td>
<td>Normalization of 82% vs 58%</td>
</tr>
</tbody>
</table>

- All trials showed some benefit…but…
- All have relatively small sample size and no long-term follow-up data available, therefore no evidence for duration of effect

*Parkes et al, Am J Gastroenterol 2008; 103: 1557–67*
Effect of Rifaximin in Patients With Bloating Without SIBO

Overall Study Population

- Rifaximin (n=63)
- Placebo (n=61)

Global endpoint: symptom improvement

P < 0.05

IBS only

- Rifaximin (n=63)
- Placebo (n=61)

Rifaximin 400mg bid x 10 days; post-tx:10 days

Global endpoint: symptom improvement

* P ≤ 0.05

Shahara AI et al. Am J Gastroenterol. 2006; 101:326
Antibiotics: Rifaximin for IBS

- Limitations: modest sample size, short duration, most patients from 1 center
- Additionally, rifaximin group had higher level of pain at baseline

Antibiotics: Rifaximin for IBS with Diarrhea or Bloating

**Phase II double-blind multicenter trial of 388 IBS-D patients (Rome II)**

- **Global Symptoms**
  - After 4 weeks: Placebo 43, Rifaximin 53 (*P < 0.05*)
  - After 12 weeks: Placebo 51, Rifaximin 59 (*P < 0.05*)

- **Bloating**
  - After 4 weeks: Placebo 42, Rifaximin 50 (*P < 0.05*)
  - After 12 weeks: Placebo 51, Rifaximin 62 (*P < 0.05*)

**Side effects:** well tolerated with no significant differences in adverse events compared to placebo

**No data available on long-term safety and effectiveness of nonabsorbable antibiotics for IBS**

ACG Task Force: Management of IBS-C: Antibiotics

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</thead>
<tbody>
<tr>
<td>Non-absorbable antibiotics: A short term course is more effective than placebo for bloating. There are no data available to support their long term safety and effectiveness for the management of IBS symptoms</td>
<td>Grade 1B</td>
</tr>
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ACG IBS Task Force, Am J Gastro 2009; 104 (S1): S1-S35
What are the therapies for IBS with diarrhea?
Pharmacologic Treatment Options in IBS

**Abdominal pain/discomfort**
- Antispasmodics
- Antidepressants
  - TCAs / SSRIs
- Alosetron

**Bloating / distension**
- Probiotics
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**Altered bowel function**
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**Diarrhea**
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**Constipation**
- Fiber
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- Lubiprostone

References:
- Drossman DA et al. Gastroenterology 2002; 123:2108
- Saad R, Chey WD. Expert Opinion Invest Drugs 2008;17:117
Antidiarrheals for IBS-D

• Loperamide is the only antidiarrheal studied in IBS

• Three RCTs of low-intermediate quality

• Decreased stool frequency and improved stool consistency but not abdominal pain or global IBS symptoms

• Most appropriate for patients with diarrhea-predominant symptoms

Brandt LJ et al. Am J Gastroenterol 2002; 97 suppl:S7
Alosetron

- 8 large placebo controlled RCTs
- Alosetron demonstrated superiority to placebo for abdominal pain, urgency, stool frequency and adequate relief of IBS symptoms
- More effective vs placebo for abdominal pain in men with non-constipated IBS (53% vs 40%, p<0.001)
- Benefit risk profile is most favorable in women with severe IBS with diarrhea who have not responded to conventional therapy (Grade 1B)
Alosetron Improves Global Symptoms in Women with Severe IBS-D


GIS Responders

% GIS Responders

Placebo N=176
0.5mg qd N=177
1mg qd N=175
1mg bid N=177

* P<0.02 vs placebo
Assessment at 12 weeks
GIS = Global Improvement Scale
Long-Term Efficacy with Alosetron


% With Adequate Relief

(Diarrhea-Predominant) (LOCF)

Follow-up

Treatment

Alosetron (n=279)

Placebo (n=290)
P<0.05

Months

Safety Profile of Alosetron

- 8 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]. GlaxoSmithKline; 2006
Indications for Restricted Use of Alosetron

- Only for women with severe IBS-D who have
  - Chronic IBS symptoms ($\geq 6$ months)
  - No evidence of anatomic or biochemical abnormalities of the GI tract
  - Failed to respond to conventional therapy

- IBS is severe if it includes diarrhea and $\geq 1$ of the following:
  - Frequent, severe abdominal pain / discomfort
  - Frequent bowel urgency or fecal incontinence
  - Disability or restriction of daily activities due to IBS

Harris LA, Chang L. Women’s Health 2007; 3:15
Conclusions

• Current pharmacological treatments are aimed at treating the predominant IBS symptom

• Strong evidence is lacking in many of the treatments currently used in IBS
What are the emerging therapies for IBS?
## Emerging therapies for IBS-C

<table>
<thead>
<tr>
<th>Agent</th>
<th>Findings</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linaclotide (guanylate cyclase C agonist)</td>
<td>Benefits for global &amp; individual IBS symptoms</td>
<td>Phase III complete</td>
</tr>
<tr>
<td>Prucalopride and TD-5108 (5-HT₄ agonists)</td>
<td>Increases stool frequency more than placebo in CC</td>
<td>Studies in IBS-C?</td>
</tr>
<tr>
<td>A3309 (selective IBAT inhibitor)</td>
<td>Preclinical studies suggest a role for CC/IBS-C</td>
<td>Phase IIa</td>
</tr>
<tr>
<td>DDP-733 (5-HT₃ agonist)</td>
<td>Benefits for subjective global assessment of IBS vs placebo</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

ACG IBS Task Force, Am J Gastro 2009; 104 (S1): S1-S35
**GC-C agonist:** Linaclotide for Stool Frequency and Abdominal Pain in IBS-C

*Phase II dose-ranging RCT of 419 IBS-C patients (Rome II)*

**Complete Spontaneous Bowel Movements/week**
- Placebo: 1
- 75 µg: 2.9
- 150 µg: 2.5
- 300 µg: 3.6
- 600 µg: 2.7

**Relief of Abdominal Pain (LS Mean Change from Baseline)**
- Placebo: -0.5
- 75 µg: -0.7 - 0.7
- 150 µg: -0.9 - 0.9
- 300 µg: -0.9 - 0.9
- 600 µg: -0.9 - 0.9

*P < 0.05 throughout*

Phase 3 trial of a selective CCK-1 antagonist dexloxeiglumide in IBS-C

Whorwell et al, Gastroenterology 2008; 134: Abstract 1051

- Significant differences between dexloxeiglumide and placebo seen for abdominal pain (p=0.001), bloating (p=0.001), straining (p=0.038), stool frequency (p=0.002), laxative use (p=0.011)

- Dexloxeiglumide demonstrated sustained relief of symptoms in females with IBS-C

Responders at 24 weeks (%)

Placebo (n=184 females)

Dexloxeiglumide 200 mg tid (n=175 females)

***p=0.003 vs placebo

No beneficial effect observed in males
Partial 5-HT₃ Agonist DDP733 for IBS-C

4-week multicenter dose-ranging RCT of 91 IBS-C patients (Rome II criteria)

Overall Responders (%)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>0.2 mg</th>
<th>0.5 mg</th>
<th>0.8 mg</th>
<th>1.4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.4</td>
<td>27.3</td>
<td>26.7</td>
<td>21.4</td>
<td>53.8</td>
</tr>
</tbody>
</table>

† Overall global assessment of relief of IBS
* P < 0.05

# Emerging therapies for IBS-D

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<thead>
<tr>
<th>Agent</th>
<th>Findings</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arverapamil</td>
<td>Benefits for global and individual symptoms in IBS-D</td>
<td><em>Phase III underway</em></td>
</tr>
<tr>
<td>Dextofisopam</td>
<td>Benefits for global and individual symptoms in IBS-D</td>
<td><em>Phase IIb underway</em></td>
</tr>
<tr>
<td>Crefelomer</td>
<td>Benefits for pain in phase II</td>
<td><em>Phase IIb planned</em></td>
</tr>
<tr>
<td>Asimadoline (periph κ-opioid agonist)</td>
<td>Benefits for global symptoms and pain in IBS-D</td>
<td><em>Phase II completed</em></td>
</tr>
</tbody>
</table>
**Ca Channel Blocker: R-verapamil Phase II Results for Non-C IBS**

<table>
<thead>
<tr>
<th>Primary Endpoints - ITT</th>
<th>Arverapamil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Global Impression</td>
<td>56.9%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Odds Ratio = 2.8, p &lt; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relief of Pain/discomfort</td>
<td>56.9%</td>
<td>43.8%</td>
</tr>
<tr>
<td>Odds Ratio = 1.95, p &lt; 0.10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N = 129 non-C IBS pts by Rome II, 7 Centers in Europe
12 week randomized, placebo controlled dose-escalation study
71% female, 100% Caucasian

Quigley et al. ACG 2007
CFTR: Crofelemer for Abdominal Pain in IBS-D

- Extracted from the Croton lechleri tree (South America)
- Antisecretory effects, suggested to occur via inhibition of CFTR (cystic fibrosis transmembrane conductance regulator)
- 12-week double-blind RCT in 242 IBS-D patients
  - no benefit for bowel function
  - significant improvement in proportion of pain- and discomfort-free days among female IBS-D patients

2,3-Benzodiazepine Agonist: Dextofisopam: Phase IIa Data for IBS

Asimadoline for IBS: Results from a 12 week phase IIb study

Mangel et al. DDW 08

% Months with Adequate Relief

N=596, 33% IBS-D, 37% IBS-C, 31% IBS-A
Benefits for pain, urgency, bloating and diarrhea seen in IBS-D
No benefits for IBS-C

Asimadoline doses 0.15, 0.5, 1mg bid
P≤0.022

*P=0.011
0.5 mg

*P=0.022
1 mg

Mangel et al. DDW 08
## Emerging therapies for Pain in IBS

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<td>Clonidine improved pain and diarrhea in IBS</td>
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<td><strong>Dual Noradrenergic Reuptake Inhibitor (NARI) and 5-HT₃ Antagonist</strong></td>
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<td>NK antagonists</td>
<td>Pharmacodynamic effects on visceral pain. No benefit in pts.</td>
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<td>CRF antagonists</td>
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Dual Noradrenergic Reuptake Inhibitor (NARI) and 5-HT₃ Antagonist DDP225 for Abdominal Pain in IBS-D

**Phase II trial of 87 female IBS-D patients (Rome II criteria)**

Adequate Response (AR) defined as at least 2 positive responses in the last 4 weeks to the question, “In the last 7 days, have you had adequate relief of your IBS pain or discomfort?”

Conclusions

- Current pharmacological treatments are aimed at treating the predominant IBS symptom
- Strong evidence is lacking in many of the treatments currently used in IBS
- The future looks promising for additional pharmacological treatments in IBS