Jointly sponsored by Purdue University College of Pharmacy and the Gi Health Foundation.
This activity is supported by Salix Pharmaceuticals, Inc.
Special thanks to our supporter for providing an educational grant:

Salix Pharmaceuticals, Inc.
LACTOSE and IBS
Lactose Intolerance in Patients With Diarrhea Predominant Irritable Bowel Syndrome is Associated With Mucosal Immune Activation and Anxiety

Yang J et al. Abstract 596
Design

• **Objective**
  – Explore association between visceral hypersensitivity induced by lactose intolerance, mucosal immune activation, and psychological factors

• **Subjects**
  – 55 IBS outpatients, 18 healthy volunteers

• **Methods**
  – Evaluation of psychological status by Hospital Anxiety and Depression Scale (HADS) and Life Events Scale (LES)
  – Lactose hydrogen breath test
  – Colonscopy with biopsies and assessment of immune cell counts
  – Assessment of rectal sensitivity
  – Assessment of cytokine levels
Results

- D-IBS patients were more anxious than healthy volunteers ($P<.001$)
- Lactose malabsorption prevalence was ~90% in all groups
  - Intolerance more prevalent in D-IBS patients 45.5% vs 16.7%, $P=.029$)
- Lactose reduced rectal discomfort thresholds in lactose intolerant patients but not in lactose malabsorption patients or healthy volunteers ($P<.001$)
- Mast cells and enterochromaffin cells were elevated in the terminal ileum in lactose intolerant patients compared to lactose malabsorption patients and healthy volunteers ($P<.001$)
- Serum TNF-α in lactose intolerant patients was significantly higher than in other groups
- Mast cells in terminal ileum (OR=1.25, $P=.004$), depression (OR=1.724, $P=.026$) were risk factors for occurrence of lactose intolerance
- Severity (TSS) of LI was associated with visceral hypersensitivity to rectal distension induced by LM, ($P=.003$), mast cells in terminal ileum ($P=.002$), and anxiety ($P=0.011$)
Conclusions

• Induction of symptoms and visceral hypersensitivity by lactose ingestion in D-IBS patients with LM is associated with mucosal immune activation and psychiatric disease

• These findings provide insight into the mechanism by which poorly fermentable carbohydrates, such as lactose in LM patients, cause symptoms in D-IBS and may identify a phenotype that may respond to dietary management and specific medical treatments
DRUG THERAPY and IBS
A3309, an Ileal Bile Acid Transport (IBAT /ASBT) Inhibitor, Significantly Improved Stool Frequency and Other Constipation-Related Complaints in Adults With Chronic Constipation: Data From an 8-Week, Randomized, Double-Blind, Placebo-Controlled Study

Chey WD et al. Abstract 10
Design

- **Objective**
  - Assess effects of A3309 in adults with chronic constipation
- **Design**
  - Phase 2, 8-week, randomized, double-blind, placebo-controlled
- **Patients (N=190)**
  - Adults with chronic constipation
  - IBS patients excluded
- **Treatments**
  - A3309 (3 groups: 5, 10, 15 mg/d)
  - Placebo
  - 8 weeks of treatment
## Results

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>5 mg</th>
<th>10 mg</th>
<th>15 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in SBM Week 1</td>
<td>1.7 ± 0.50</td>
<td>2.5 ± 0.52</td>
<td>4.0 ± 0.52**</td>
<td>5.4 ± 0.51#</td>
</tr>
<tr>
<td>Change from baseline – SBM overall Wks 1-8</td>
<td>1.5 ± 0.47</td>
<td>2.6 ± 0.47</td>
<td>3.1 ± 0.47*</td>
<td>4.6 ± 0.47#</td>
</tr>
<tr>
<td>Change from baseline – CSBM overall Wks 1-8</td>
<td>1.0 ± 0.43</td>
<td>2.4 ± 0.43*</td>
<td>2.5 ± 0.43**</td>
<td>4.1 ± 0.43#</td>
</tr>
<tr>
<td>Time (hrs) to first SBM/CSBM (median;95% CI)</td>
<td>27(20-44) 171(112-360)</td>
<td>23(17-29) 108 (51-270)</td>
<td>12(7-23)* 54 (27-119)*</td>
<td>7(5-20)* 23 (9-43)**</td>
</tr>
<tr>
<td>Overall Constipation Response</td>
<td>3%</td>
<td>15%</td>
<td>33%</td>
<td>44%</td>
</tr>
<tr>
<td>C4 Change from baseline (ng/mL)</td>
<td>1.2 ± 4.26</td>
<td>14.9 ± 3.96</td>
<td>21.1 ± 4.48**</td>
<td>12.9 ± 5.13*</td>
</tr>
<tr>
<td>LDL Cholesterol % change from baseline</td>
<td>+ 2</td>
<td>- 2</td>
<td>- 13**</td>
<td>-10**</td>
</tr>
</tbody>
</table>
Conclusions

• A3309 improved stool frequency and other constipation-related complaints in patients with CIC

• The effect was dose-dependent with the 10 mg dose offering the best balance of efficacy and tolerability

• Reduced LDL cholesterol is an added benefit of treatment

Spiegel BM et al. DDW 2010; abstract no. 733.
Effects of A3309, an Ileal Bile Acid Transporter Inhibitor, on Colonic Transit and Symptoms in Patients with Functional Constipation

Wong BS et al. Abstract 908
Design

- **Objective**
  - Examine effects of A3309 (small molecule inhibitor of ileal bile acid transporter [IBAT]) in patients with functional constipation

- **Design**
  - Double-blind, placebo-controlled study

- **Subjects**
  - 36 female functional constipation patients

- **Treatments (14 days)**
  - Placebo
  - A3309 15 mg once daily
  - A3309 20 mg once daily

- **Key Assessments**
  - GI and colonic transit of solids by validated scintigraphic methods
  - Stool consistency
  - Symptoms of constipation
# Results

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=13</th>
<th>A3309 15mg N=11</th>
<th>A3309 20mg N=12</th>
<th>Overall treatment effect ANCOVA p=value*</th>
<th>Dunnett’s test: each A3309 dose vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo N=13</td>
<td>A3309 15mg N=11</td>
<td>A3309 20mg N=12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overall treatment effect ANCOVA p=value*</td>
<td>Dunnett’s test: each A3309 dose vs. placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonic transit GC at 24h</td>
<td>1.93±0.15</td>
<td>2.72±0.4</td>
<td>3.18±0.43</td>
<td>0.059</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonic transit GC at 48h</td>
<td>2.75±0.18</td>
<td>4.13±0.33</td>
<td>4.46±0.24</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending colon emptying t1/2 (h)</td>
<td>14.8±1.6</td>
<td>14.0±3.6</td>
<td>5.8±1.9</td>
<td>0.084</td>
<td>0.098</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool consistency (BSF Scale 1-7)</td>
<td>2.69±0.24</td>
<td>4.17±0.32</td>
<td>4.42±0.32</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool frequency (daily)</td>
<td>1.43±0.24</td>
<td>1.33±0.15</td>
<td>2.14±0.39</td>
<td>0.091</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ease of stool passage (scale 1-7)</td>
<td>3.49±0.12</td>
<td>4.26±0.17</td>
<td>4.49±0.21</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strain score [scale 1 (none) = 5 (extreme amount)]</td>
<td>2.29±0.21</td>
<td>1.67±0.11</td>
<td>1.71±0.19</td>
<td>0.038</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compared to before start of study, rating of constipation during the days of treatment (scale 1-7)+</td>
<td>3.8±0.3</td>
<td>3.3±0.3</td>
<td>2.0±0.3</td>
<td>0.001</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment effectiveness (scale 1-5)+</td>
<td>4.3±0.3</td>
<td>3.7±0.3</td>
<td>2.4±0.4</td>
<td>0.002</td>
<td>0.053</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean daily abdominal discomfort score (scale 1-5)+</td>
<td>2.2±0.2</td>
<td>1.7±0.2</td>
<td>2.0±0.3</td>
<td>0.12</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean daily abdominal bloating score (scale 1-5)+</td>
<td>2.5±0.3</td>
<td>1.7±0.2</td>
<td>1.8±0.2</td>
<td>0.096</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Spiegel BM et al. *DDW 2010* ; abstract no. 865.
Conclusions

• A3309 accelerates colonic transit without significant changes in gastric emptying or small bowel transit

• A3309 induced loosened stool consistency with beneficial effects on ease of passage and straining scores

• In addition, there were significant effects on reduction of constipation severity and bloating and patients perceived effectiveness of A3309 treatment

• These data support the potential use of A3309 in the treatment of patients with functional constipation
Lubiprostone Treatment in Patients With Irritable Bowel Syndrome With Constipation for up to 16 Weeks Duration

Panas RM, Ueno R. Abstract Mo1308
Design

• Objective
  – Evaluate abdominal and bowel symptoms through 16 weeks, including a 4-week randomized withdrawal of treatment

• Design
  – Randomized, double-blind, placebo-controlled

• Patients (N=258)
  – IBS-C (modified ROME II criteria)

• Treatments
  – Period 1: 12 weeks of treatment with once-daily lubiprostone 8ug or placebo
  – Period 2: 4-week randomized withdrawal period
Results

• Mean changes from baseline at all treatment weeks were statistically significant in all treatment groups for stool consistency, abdominal discomfort/pain, and SBM frequency ($P<.003$)

• Lubiprostone was associated with a statistically significant improvement in stool consistency compared with placebo at ~50% of weekly visits ($P<.03$)
  – Similar significant improvements were observed at Weeks 13, 14, and 15 for patients who continued to receive lubiprostone ($P<.05$)

• Patients who received lubiprostone experienced a statistically significant mean reduction from baseline in abdominal discomfort/pain at Weeks 10 and 11 compared to placebo group ($P<.05$)
  – Significant results were further observed at Weeks 13, 15, and 16 for patients who continued to take lubiprostone ($P<.04$)
Conclusions

- Lubiprostone provided significant improvement in stool consistency, abdominal discomfort/pain, and SBM frequency for standard treatment of 12 weeks

- Longer-term treatment provides significant reductions in abdominal discomfort/pain
A Randomized, Open Labeled, Multicenter Clinical Trial on the Effectiveness and Safety of the 5-HT3-Receptor Antagonist Ramosetron in Male Patients With Irritable Bowel Syndrome With Diarrhea: Comparison With Mebeverine

Lee KJ, Rhee P-L. Abstract Mo1302.
Design

• Objective
  – Evaluate the efficacy and safety of ramosetron in men with IBS-D

• Design
  – Double-blind, multicenter, randomized clinical trial

• Patients (N=297)
  – IBS-D by Rome III criteria

• Treatments
  – Ramosetron 5 µg/d once daily
  – Mabeverine 135 mg three times daily

• Treatment duration: 4 weeks


Results

• Efficacy
  – Responder rate at week 4 was 36% for ramosetron
  – Frequency of defecation was significantly reduced by ramosetron treatment (from 2.0 times/day at 1 week to 1.8 times/day at 4 week, $P= .016$) but not significantly altered by mebeverine treatment
  – Ramosetron provided greater improvement in QoL than mebeverine

• Safety
  – Twelve patients (7.9%) in the ramosetron group and 6 patients (4.1%) in the mebeverine group reported adverse effects ($P= .266$)
  – Drug-related adverse events with a frequency >1% in the ramosetron group were constipation and abdominal discomfort
  – Ischemic colitis and severe constipation were not reported by any patients
Conclusions

• Ramosetron hydrochloride 5 µg/d was effective and well-tolerated as treatment for abdominal pain, discomfort and abnormal bowel habits in male patients with D-IBS, compared with mebeverine 135 mg three times daily
Efficacy and Safety of Once-Daily Linaclotide Administered Orally for 26 Weeks in Patients With IBS-C: Results From a Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial

Chey WD et al. Abstract 837
Design

- Objective
  - Assess efficacy and safety of linaclotide 266 µg once daily for 26 weeks in patients with IBS-C
- Patients (N=804)
  - Adults with IBS-C (Rome III criteria)
- Methods
  - Randomized, double-blind, placebo-controlled trial
- Treatments
  - Linaclotide 266 µg
  - Placebo
## Results

<table>
<thead>
<tr>
<th>Responder (% Patients)</th>
<th>12 Weeks</th>
<th>26 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO</td>
<td>LIN</td>
</tr>
<tr>
<td><strong>Primary Endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30% abdominal pain reduction, ≥3 CSBM, increase ≥1 CSBM from baseline; in the same week</td>
<td>3.0</td>
<td>12.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥3 CSBM, increase ≥1 CSBM from baseline; in the same week</td>
<td>5.0</td>
<td>18.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥30% abdominal pain reduction</td>
<td>19.6</td>
<td>38.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Responder per FDA March 2010 draft guidance (% Patients)&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥6 of 12 weeks (% patients)</td>
<td>13.9</td>
<td>33.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>P≤.001 vs placebo; <sup>b</sup>Guidance for Industry: Irritable Bowel Syndrome - Clinical Evaluation of Products for Treatment; <sup>c</sup>For the % Abdominal Pain-free Days secondary endpoint, mean change from baseline is presented and the ANCOVA is based on rank-transformed data; <sup>d</sup>P=.0003
Results (Continued)

<table>
<thead>
<tr>
<th></th>
<th>12 Weeks</th>
<th>26 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO</td>
<td>LIN</td>
</tr>
<tr>
<td><strong>Primary Endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responder (% Patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30% abdominal pain reduction</td>
<td>34.5</td>
<td>48.9a</td>
</tr>
<tr>
<td>≥1 CSBM</td>
<td>22.6</td>
<td>47.6a</td>
</tr>
<tr>
<td><strong>Individual (LS Mean Change from Baseline)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain (0-10 scale)</td>
<td>-1.1</td>
<td>-1.9a</td>
</tr>
<tr>
<td>Abdominal discomfort (0-10 scale)</td>
<td>-1.1</td>
<td>-1.9a</td>
</tr>
<tr>
<td>Bloating (0-10 scale)</td>
<td>-1.0</td>
<td>-1.9a</td>
</tr>
<tr>
<td>Straining (1-5 scale)</td>
<td>-0.7</td>
<td>-1.2a</td>
</tr>
<tr>
<td>Stool consistency BSFS: 1=hard stol, 7=watery</td>
<td>0.6</td>
<td>1.9a</td>
</tr>
<tr>
<td>CSBM/week</td>
<td>0.7</td>
<td>2.2a</td>
</tr>
<tr>
<td>SBM/week</td>
<td>1.3</td>
<td>4.0a</td>
</tr>
<tr>
<td>% Pain-free days</td>
<td>4.8</td>
<td>10.5d</td>
</tr>
</tbody>
</table>

aP≤.001 vs placebo; b Guidance for Industry: Irritable Bowel Syndrome - Clinical Evaluation of Products for Treatment; c For the % Abdominal Pain-free Days secondary endpoint, mean change from baseline is presented and the ANCOVA is based on rank-transformed data; dP=.0003
Results (Continued)

Weekly Mean Percent Change from Baseline in Abdominal Pain

Mean ± 95% confidence interval

$P < .001$ for linaclotide vs placebo for all weeks

Trial Week

Treatment Groups

- 266 µg
- Placebo
Conclusions

- Linaclotide produced statistically significant improvements in abdominal and bowel symptoms in IBS-C patients that were sustained over 26 weeks of treatment.

- Diarrhea was the most common AE:
  - 4% of linaclotide patients vs 0.2% of placebo patients discontinued due to diarrhea.
Effect of Linaclotide on Quality of Life in Adults With Irritable Bowel Syndrome With Constipation: Pooled Results From Two Randomized, Double-Blind, Placebo-Controlled Phase 3 Trials

Carson R et al. Abstract 223
Design

- **Objective**
  - Assess effect of linaclotide on quality of life in adults with IBS
- **Design**
  - Two phase 3 randomized, placebo-controlled trials
- **Patients (N=1490)**
  - IBS-C by Rome II criteria
- **Treatments**
  - Linaclotide 266 µg
  - Placebo
- **Treatment duration: 12 weeks**
## Results

### LS Mean Change from Baseline to Week 12 for IBS-QOL Scores

<table>
<thead>
<tr>
<th>IBS-QOL Scale</th>
<th>Placebo (n=742)</th>
<th>Linaclotide 266 µg (n=748)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>LS Mean Change from Baseline to Week 12</td>
</tr>
<tr>
<td>Overall (P)</td>
<td>61.90</td>
<td>13.10</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>63.58</td>
<td>15.17</td>
</tr>
<tr>
<td>Interference with activity</td>
<td>68.81</td>
<td>11.33</td>
</tr>
<tr>
<td>Body image</td>
<td>49.29</td>
<td>15.65</td>
</tr>
<tr>
<td>Health worry</td>
<td>46.21</td>
<td>17.93</td>
</tr>
<tr>
<td>Food avoidance</td>
<td>50.25</td>
<td>12.73</td>
</tr>
<tr>
<td>Social reaction</td>
<td>67.23</td>
<td>11.10</td>
</tr>
<tr>
<td>Sexual</td>
<td>69.12</td>
<td>10.38</td>
</tr>
<tr>
<td>Relationships</td>
<td>73.15</td>
<td>8.46</td>
</tr>
</tbody>
</table>
Conclusions

• Compared to placebo, once-daily linaclotide treatment for 12 weeks significantly improved:
  – Overall QOL and seven out of eight important QOL domains as measured by the IBS-QOL, in adults with IBS-C using data pooled across 2 Phase 3 trials
Efficacy of Antidepressants in Irritable Bowel Syndrome: An Updated Systematic Review and Meta-Analysis Controlling for Depression

Ford AC et al. Abstract Sa1035
Design

• Objective
  – Examine the efficacy of antidepressant drugs, controlling for coexisting depression

• Design
  – Meta-analysis

• Patients (N=1022)
  – 554 received antidepressants

• Treatments
  – 9 randomized controlled trials of tricyclic antidepressants
  – 6 randomized controlled trials of SSRIs
  – 1 randomized controlled trials including both tricyclic antidepressants and SSRIs
Results

• When the 10 RCTs comparing TCAs to placebo were pooled:
  – 166 (43.9%) of 378 had persistent symptoms, compared to 189 (62.2%)
    of 304 receiving placebo (RR=0.70; 95% CI 0.60 to 0.83)

• In the 5 RCTs of SSRIs:
  – 76 (43.2%) of 176 patients allocated to SSRIs with persistent symptoms,
    compared to 125 (69.4%) of 180 placebo patients (RR=0.63; 95% CI 0.44
    to 0.91)

• When only the four RCTs that screened for and excluded
  depressed individuals were included in the analysis:
  – RR of symptoms persisting was 0.73 (95% CI 0.47 to 1.15), compared
    with a RR of 0.65 (95% CI 0.55 to 0.78) in the other 12 trials
  – Not statistically significant (Cochrane Q=0.64)
Conclusions

• Evidence continues to accumulate for the efficacy of antidepressants in the treatment of IBS

• Part of the beneficial effect may stem from the treatment of coexistent depression

• More RCTs examining their efficacy in non-depressed IBS patients are required to clarify this issue
MICROFLORA and IBS
Effect of Probiotic Treatment on Visceral Hypersensitivity in Irritable Bowel Syndrome

Thijssen A et al. Abstract Tu1869
Design

- **Objective**
  - Assess the effect of probiotic treatment on visceral hypersensitivity

- **Design**
  - Randomized, placebo-controlled, double-blind trial

- **Patients (N=21)**
  - IBS by Rome II criteria

- **Treatments**
  - *Lactobacillus casei* Shirota (2 bottles daily, $6.5 \times 10^9$ CFU/bottle)
  - Placebo

- **Treatment duration: 8 weeks**
Results

- Rectal compliance did not differ significantly before or after treatment in either group.
- Perception of urge during highest pressures (32-40 mm Hg) decreased significantly by study end point (65±27 mm to 53 ± 23 mm; \( P < .05 \))
  - No change in placebo group.
- Pain scores at higher pressures were not different between placebo and treatment groups.
Conclusions

• Treatment with *Lactobacillus casei* did not affect pain perception but beneficially and significantly influenced urge perception scores
Time to Onset and Durability of Relief in Non-Constipation IBS Patients Over 12 Weeks Following a 2-Week Course of Rifaximin

Chey WD et al. Abstract Mo1299
Design

• Objective
  – Examine time to onset and durability of relief with rifaximin vs placebo for non-C IBS symptoms over 12 weeks

• Patients
  – Non-constipation IBS
  – Included studies from pivotal TARGET 1 and 2 studies

• Methods
  – Efficacy analysis performed by comparing the number of times patients were responders with rifaximin and placebo patients using ordered logistic regression at biweekly intervals up to 12 weeks
Results

- Significantly more rifaximin patients achieved adequate relief of weekly global IBS symptoms and IBS-related bloating vs placebo at all biweekly intervals from week 2 through week 12 ($P \leq 0.0154$, $P \leq 0.0198$, respectively).
- Responders by daily symptom severity measures for global IBS symptoms, bloating, abdominal pain, and abdominal pain and stool consistency showed statistical significance favoring rifaximin for the combined data at all biweekly intervals up to week 12 ($P \leq 0.0225$).
- Analysis of each individual study showed statistical significance for each of these endpoints at most of the biweekly intervals.
- The safety profiles were similar between groups.
Conclusions

- A 14-day course of rifaximín 550 mg TID demonstrated statistically-significant onset of relief as early as week 2 and durable relief up to week 12 across endpoints in patients with non-C IBS
Efficacy of Rifaximin in Patients With Irritable Bowel Syndrome: A Meta-Analysis

Menees SB et al. Abstract 215
Design

• Objective
  – Examine the efficacy of rifaximin in patients with IBS

• Design
  – Meta-analysis

• Patients (N=1803)
  – 5 studies included in the analysis
  – 96% non-constipated IBS
Results

Meta-analysis of 5 trials of rifaximin vs placebo (N=1803)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Response rates (%)</th>
<th>OR</th>
<th>95%CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rifaximin</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Symptoms</td>
<td>42</td>
<td>32</td>
<td>1.57</td>
<td>[1.29,1.91]</td>
</tr>
<tr>
<td>Bloating</td>
<td>42</td>
<td>32</td>
<td>1.55</td>
<td>[1.27,1.89]</td>
</tr>
</tbody>
</table>

- Serious AEs with rifaximin were rare (<2%) and similar to placebo
- No confirmed reports of *C difficile-associated diarrhea*
Conclusions

• In high quality studies, rifaximin was more effective than placebo at improving global symptoms and bloating in patients with IBS

• Rifaximin was well tolerated in short term trials

• Efficacy and safety data beyond 10 weeks of therapy are not available
Post-Infectious Irritable Bowel Syndrome Following a Water-Borne Norovirus-Enterovirus Gastroenteritis Outbreak

Zanini B et al. Abstract Su1990
Design

• Background
  – In 2009, there was an outbreak of viral gastroenteritis associated with contamination of municipal drinking water
  – This study assessed the incidence of functional gastrointestinal disorders at 12 months after the outbreak

• Subjects (N=353)
  – Residents of San Felice del Benaco (Italy)
Results

Patients (n=185) vs. Controls (n=168)

<table>
<thead>
<tr>
<th>Condition</th>
<th>GSRS Score</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>2</td>
<td>.0002</td>
</tr>
<tr>
<td>Reflux</td>
<td>1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Indigestion</td>
<td>1</td>
<td>.0005</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>.0001</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Conclusions

• This study provides evidence that mixed Norovirus and Enterovirus GE may lead to postinfectious GI disorders that persist for >12 months after infection

• PI-IBS following viral infections develops in a substantial proportion of patients (22%) similar to that reported after bacterial GE
Predictive Factors in the Development of Post-Infectious Irritable Bowel Syndrome

Wong RK et al. Abstract Su1989
Design

• Objective
  – Assess risk factors for post-infectious IBS

• Subjects (N=738)
  – Adults reported to Department of Health and Human Services in North Carolina with confirmed bacterial gastroenteritis

• Methods
  – Questionnaire
  – Oragene kit (saliva collection/genetic testing)
## Results

<table>
<thead>
<tr>
<th></th>
<th>PI-IBS (n=93)</th>
<th>Controls (n=141)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% females)</td>
<td>61.3%</td>
<td>36.9%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.36 ± 17.36</td>
<td>47.81 ± 16.63</td>
<td>.016</td>
</tr>
<tr>
<td>Somatization T-score</td>
<td>57.31 ± 10.23</td>
<td>50.10 ± 9.34</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Depression T-score</td>
<td>52.64 ± 12.21</td>
<td>49.65 ± 10.50</td>
<td>.084</td>
</tr>
<tr>
<td>Anxiety T-score</td>
<td>52.38 ± 11.13</td>
<td>47.14 ± 8.85</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>General Severity Index</td>
<td>55.71 ± 10.40</td>
<td>48.82 ± 10.45</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vomiting during GE (%)</td>
<td>47.3%</td>
<td>45.3%</td>
<td>.435</td>
</tr>
<tr>
<td>Diarrhea during GE (%)</td>
<td>96.8%</td>
<td>97.1%</td>
<td>.584</td>
</tr>
<tr>
<td>Pain during GE (%)</td>
<td>97.8%</td>
<td>83.9%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abd distention during GE (%)</td>
<td>79.3%</td>
<td>49.6%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mucus in stools during GE (%)</td>
<td>70.3%</td>
<td>57.5%</td>
<td>.034</td>
</tr>
</tbody>
</table>
Conclusions

• This study replicates previous reports that female gender, anxiety, and somatization (similar to hypochondriasis) are risk factors that predispose to the development of PI-IBS

• GI symptoms of pain, distention, and mucus during the GE episode were also significantly associated with PI-IBS

• Significant independent predictors were gender, psychological distress and distention
Saccharomyces Cerevisiae CNCM I-3856 Reduces Digestive Discomfort and Abdominal Pain in Subjects With Irritable Bowel Syndrome: A Randomized Double-Blinded Placebo-Controlled Clinical Trial

Desreumaux P et al. Abstract 217
Design

- **Objective**
  - Assess effects of *S. cerevisiae* in subjects with IBS
- **Patients (N=179)**
  - Adults with IBS (Rome III criteria)
- **Methods**
  - Randomized, double-blind, placebo-controlled trial
- **Treatments**
  - *S. cerevisiae* CNCM I-3856 (N=86)
  - Placebo (N=93)
  - 8 weeks of treatment, followed by 3-week washout period
Results

- The proportion of responders was significantly higher \((P=0.04)\) in the treated group versus the placebo group (63% vs 47%, OR = 1.88, 95%, CI: 0.99-3.57) in the last 4 weeks of treatment.
- A trend toward improvement was observed with CNCM I-3856 for other IBS symptoms and for subjective global relief.
- Treatment was well tolerated, no significant effect on stool frequency, consistency, fecal calprotectin levels.
- Shift from the predominance of proteolytic to glucidolytic bacteria after 8 weeks of active treatment.
Conclusions

- *S. cerevisiae* CNCM I-3856 at 4X10^9 CFU/d delivered once daily by 1 capsule is well tolerated and reduces abdominal pain/discomfort without altering stool frequency and consistency.

- *S. cerevisiae* may be a new strategy to improve abdominal pain/digestive discomfort in subjects with irritable bowel syndrome.
Small Bowel Culture Confirms the Presence of Small Intestinal Bacterial Overgrowth in a Subset of IBS Subjects

Pyleris M et al. Abstract 930
Design

• Objective
  – Evaluate the association between SIBO and IBS using a culture technique

• Patients (N=235)
  – IBS (Rome III criteria)

• Methods
  – Quantitative culture of aspirates from the second part of the duodenum
  – SIBO defined as the presence of colonic-type bacteria at a quantity of $>10^3$ cfu/mL
Results

• SIBO present in 47 patients (20%)
  – 36.5% of IBS patients met criteria for SIBO, compared with 10.7% of non-IBS subjects ($P<.0001$)
  – Prevalence of SIBO was 57.1% in IBS-D and 30.2% among those with IBS without diarrhea
• IBS was the only factor related to the presence of SIBO (OR: 4.93; $P<.0001$)
• Other findings
  – SIBO not found in patients with H pylori infection
  – SIBO was related to lower BMI
  – Use of gastric pH-modifying drugs was not associated with SIBO
Conclusions

• This study is the first to demonstrate that SIBO is implicated in IBS using small bowel culture and an approach that controls for variables such as PPI

• SIBO appeared to be associated with a lack of HP and lower BMI as well
Comparison of Abdominal Bloating Severity Between Irritable Bowel Syndrome Patients With Low and High Hydrogen Production in Lactulose Breath Test

Lasa JS et al. Abstract Su2013
• **Objective**
  – Examine the difference in abdominal bloating in patients with low (LH2) or high (HH2) breath hydrogen production

• **Design**
  – Sequential analysis of lactulose breath tests
  – IBS assessment of symptom severity completed by all patients

• **Patients (N=234)**
  – IBS
## Results

<table>
<thead>
<tr>
<th></th>
<th>Abdominal bloating severity score</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LH2</td>
<td>HH2</td>
</tr>
<tr>
<td>All patients</td>
<td>6.86 ± 2.03</td>
<td>5.47 ± 2.6</td>
</tr>
<tr>
<td>IBS-C patients only</td>
<td>7.17 ± 1.67</td>
<td>5.94 ± 1.97</td>
</tr>
</tbody>
</table>
Conclusions

• Patients with a low hydrogen area under the curve in lactulose breath test, compatible with the predominance of hydrogen-consuming bacteria have significantly more severe abdominal bloating than those IBS patients with an elevated hydrogen pulmonary excretion, regardless of clinical pattern