Reporting on IBS

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Characteristics of US Patients with Chronic Constipation Encountered in Primary Care: Data from the Examination of Chronic Constipation Treatment and Outcomes in Everyday Medical Practice (EXCCEED) (P1168)¹

Management of Chronic Constipation: Results from the EXCCEED Registry (P771)²

1 Chey W et al. ACG 2010
2 Sun S et al. ACG 2010
Purpose

- Understand the treatment patterns of OTC and prescription medications in patients with CC encountered in primary care clinical practice
Methods

- EXCCEED registry
  - 12-month, observational, longitudinal, multi-center study in the United States
- Patients
  - Age >18 years
  - Constipation-related complaints of 3 months or more
  - Patients with a pre-existing diagnosis of IBS or moderate to severe abdominal pain/discomfort were not eligible for enrollment
Results

- 691 CC patients from 60 primary care sites were enrolled
  - Mean duration of CC related symptoms was 8.4±14.2 years
  - Time from the first complaint of CC related symptoms to initial CC related office visit was 5.5±12.4 years

- Most common symptoms:
  - Straining during defecation (93.4%)
  - Lumpy or hard stool (92.2%)
  - Sensation of incomplete evacuation (81.2%)

- Most bothersome symptoms:
  - Straining during defecation (38.2%)
  - Bloating (24.5%)
  - Lumpy or hard stool (17.0%)

- Common comorbid conditions in CC patients:
  - Hemorrhoids (19.0%), depression (15.2%), diabetes (14.3%), anxiety (12.9%), chronic pain (8.4%), diverticulosis (4.9%) fecal impaction (1.9%), and anal fissures or stenosis (1.5%).
Results

- Average time from the first complaint of CC related symptoms to first OTC therapy was $2.4 \pm 9.1$ years
- Time from first complaint of CC related symptoms to Rx therapy was $8.7 \pm 14.3$ years
# Results

<table>
<thead>
<tr>
<th>Lifestyle Modification (N=672, 97.3%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber supplement (e.g., metamucil, citrucel)</td>
<td>526</td>
<td>76.1%</td>
</tr>
<tr>
<td>Dietary fiber (i.e., from food)</td>
<td>520</td>
<td>75.3%</td>
</tr>
<tr>
<td>Dietary modification</td>
<td>381</td>
<td>55.1%</td>
</tr>
<tr>
<td>Exercise</td>
<td>221</td>
<td>32.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTC Laxatives (N=478, 69.2%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Senna, bisacodyl or polyethylene glycol</td>
<td>309</td>
<td>44.7%</td>
</tr>
<tr>
<td>Magnesium hydroxide, or magnesium citrate</td>
<td>159</td>
<td>23.0%</td>
</tr>
<tr>
<td>Stool softener (ducosate sodium)</td>
<td>150</td>
<td>21.7%</td>
</tr>
<tr>
<td>Lubricant (mineral oil, caster oil)</td>
<td>32</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other OTC Treatment (N=163, 23.6%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppositories or enemas</td>
<td>108</td>
<td>15.6%</td>
</tr>
<tr>
<td>Herbal remedies (cascara, rhubarb, aloe)</td>
<td>58</td>
<td>8.4%</td>
</tr>
<tr>
<td>Alternative therapies (acupuncture, relaxation training)</td>
<td>6</td>
<td>0.9%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Prescription (N=91, 13.2%)</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Lubiprostone</td>
<td>52</td>
<td>7.5%</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>19</td>
<td>2.7%</td>
</tr>
<tr>
<td>Tegaserod maleate</td>
<td>14</td>
<td>2.0%</td>
</tr>
<tr>
<td>Lactulose</td>
<td>7</td>
<td>1.0%</td>
</tr>
</tbody>
</table>
Key Takeaways

- CC patients enrolled in the EXCCEED registry waited over 2 years before starting a doctor-recommended OTC treatment.
- Lifestyle interventions and OTC remedies dominated the management of CC patients encountered in primary care.
- Use of prescription treatment was low and typically occurred only after many years of symptoms.
Colonic Transit Correlates with Frequency of Bowel Movements but Not Stool Form in Patients with Constipation (P342)
Purpose

• Evaluate the relationship of stool form and frequency with colonic transit in constipated patients.
Methods

• Patients
  – Underwent whole gut scintigraphy followed by anal manometry for constipation
  – Completed questionnaire on number of bowel movements per week and the BSFS

• Design
  – Whole gut transit measured at 24, 48, and 72 hours
  – Correlations were assessed between BSFS, frequency of bowel movements, colonic transit, BASP, IAS relaxation, and balloon expulsion time
Results

- A total of 171 patients, 25 males and 146 females were evaluated.
- Number of bowel movements correlated with colonic transit at 24 hours ($P=0.003$), 48 hours ($P=0.0001$), and 72 hours ($P<0.0001$).
- A correlation was seen between frequency of bowel movements and BSFS ($P<0.001$).
- There was no correlation between BSFS and:
  - Colonic transit at 24 hours
  - Colonic transit at 48 hours
  - Colonic transit at 72 hours
- Balloon expulsion time, BASP, and IAS relaxation did not correlate with frequency of bowel movements.
Key Takeaways

- Frequency of bowel movements correlates with colonic transit in patients with chronic constipation
- For the clinician, decreased number of bowel movements, rather than stool form, is associated with slow colonic transit
- *These results are contradictory to previous studies and require confirmation*
IBS Symptoms: It’s in the Genes (P340)
Purpose

- Explore a possible association of the COMT val158met polymorphism with IBS symptoms, abdominal pain, and bowel patterns
- Catechol-o-methyl transferase: inactivation of dopamine, epi, norepi
- COMT protein encoded by the gene COMT
- Val158met: Valine to methionine mutation at position 158
- Met/met: ability to experience increased rewards
Methods

• Patients
  – Women diagnosed with IBS (Rome II criteria)
  – High abdominal pain scores (Rome II A2 ≥3 and A9≥3)
  – ≥ 25% days/month with pain
• Subjects recorded symptoms in a daily diary for 28 days and also completed an SCL-90-R
• Subjects were matched against age-related controls without bowel symptoms
• DNA was isolated from buccal swabs in patients and from whole blood in controls
• COMT genotype was determined by PCR-based assay
Results

- There was no difference in Rome II abdominal pain scores between genotypes.
- Diarrhea predominance was more common in the met/met group.
- Met/met was associated with greater daily GI symptoms than val/val and val/met:
  - Abdominal discomfort after eating, $P=.017$
  - Abdominal distension, $P=.048$
  - Intestinal gas, $P=.048$
  - Flatulence, $P=.05$
  - Bloating, $P=.061$
- Met/met had a higher percentage of days with pain after eating ($P=.023$).
Key Takeaways

- This study represents an example of the evolving literature suggesting that single-nt polymorphisms may play an important role in patients with IBS.
- The met/met genotype was associated with increased GI symptoms in patients with IBS.
- There was no statistically significant difference in genotypes between IBS and control groups or Rome II abdominal pain scores among the IBS group.
  - Could be attributable to small study size and that IBS subjects were chosen for ‘high pain’ symptoms, thereby limiting variance.
Is Celiac Screening Increasing in Patients with Functional Symptoms?
(P341)
Purpose

- Evaluate whether the frequency of CD screening changed from 1/2004 to 12/2008 in patients with and without FGIDs
Methods

- Consecutive gastroenterology patients at Mayo Clinic who had screening blood work for celiac disease were identified from laboratory records.

- Charts were reviewed for:
  - Demographics
  - Provider type
  - Presence and duration of symptoms that prompted screening
  - Prior diagnosis of IBS or CD
  - Clinical impression of functional symptoms
Results

- Review of 2865 patient records
  - CD serology was positive in 4.2% of patients
  - The most common presenting symptoms were abdominal pain (40%), diarrhea (31%), dyspepsia (12%), anemia (6%), and constipation (6%)
  - IBS present in 12% of patients
  - 5% had a previous diagnosis of CD
  - Functional GI symptoms were present in 37% of all patients completing CD screening
- Females were more likely to have FGIDs compared with males [39% vs 30%; OR 1.52, 95% CI 1.28 - 1.81]
- Functional GI symptoms were present for < 1 year in 37%, 1-5 years in 30%, and for >10 years in 17%
Results

Frequency of Testing Decreased in Patients With FGIDs

F0r trend <.001
Key Takeaways

- There was an increasing frequency of screening in general
  - May reflect increased educational efforts nationally to enhance celiac disease awareness
- Celiac disease screening in IBS patients did not increase over time
- Limitations
  - Did not account for referral pattern to Mayo and pre-referral testing
The Addition of Desipramine Improves Pain Relief in Female Patients Taking Alosetron for IBS-D (P333)
Purpose

- Explore the efficacy of adding desipramine to alosetron to control pain
- Desipramine was chosen over other tricyclics given its lower anticholinergic effect compared to other drugs in that class
Methods

- IBS registry reviewed for female patients taking alosetron for IBS-D
- Design
  - Open-label with intention to treat
- Inclusion criteria
  - Stable dose of alosetron for 60 days
  - Pain or discomfort 3 or more days per week
- Treatment
  - Desipramine started at 10 mg daily and increased by 10 mg monthly until symptom relief or a side effect was seen
- Follow-up
  - After initial visit, follow-up was arranged at 3, 6, 9 and 12 months
- End points
  - The primary objectives were pain relief and absence of side-effects
Results

• 20 patients enrolled in and completed the study
• No significant constipation, ischemic colitis or other side-effects were observed
• 4 patients had complete resolution of pain on 10 mg; 8 on 20 mg; and 3 on 30 mg
• 5 patients had partial relief with discomfort observed at ≤1 episode per week
• Mean time to symptom resolution was 2 weeks after optimal dose was achieved
Key Takeaways

- Addition of desipramine to alosetron may improve pain control in female patients with IBS-D
- Limitations
  - Uncontrolled, small study
Alosetron Treatment Led to Fewer Physician Contacts and Fewer Days of Lost Work Productivity Compared to Treatment with Traditional Therapy for Diarrhea-Predominant IBS (IBS-D) (P345)
Purpose

- To compare the impact of alosetron treatment with that of conventional therapy for IBS-D on healthcare resource use, productivity, and quality of life
Methods

- Patients
  - Female patients with IBS-D

- Design
  - Randomized, open-label study to evaluate health care resource use, QoL, and productivity

- Treatment
  - Alosetron (1 mg BID) versus conventional therapy for 24 weeks

- End points
  - Number of physician contacts
  - Number of medications used during the treatment period
  - Global Improvement Scale
  - IBS-related QoL instrument
  - Total Lost Work Productivity was computed as: Days missed due to IBS + (Total days with IBS symptoms * (1 - % Effectiveness))
Results

- 2456 patients/2256 evaluable
- Alosetron-treated patients:
  - Fewer physician contacts ($P=0.032$) for any health problem
  - Used fewer medications on average (9.1 vs. 9.5)
  - Greater improvement in all 9 domains of the IBS-QoL ($P<0.001$)
  - Greater response rates on GIS ($P<0.001$)
- Conventional therapy patients:
  - Missed more work days (3.0 vs 1.9 days; $P<0.001$)
  - Lost more days of productivity (5.0 vs 3.2 days, $P<0.001$)
- With the exception of constipation and GI pain and discomfort, the incidence of other AEs was similar in both groups
Alosetron therapy led to significantly greater improvements in IBS symptoms and QoL compared to conventional therapy.

Subjects treated with conventional therapy:
- Used more healthcare resources in terms of physician time
- Missed more days of work
- Reported significantly greater lost productivity time
Week 1 Changes in Bowel and Abdominal Symptoms Following Linaclotide Treatment: Results from Two Phase 3 Trials in Chronic Constipation Patients (P1171)
Purpose

• Determine time to onset of symptom changes following treatment initiation in Phase 3 trials
Methods

• Patients (N=1272)
  – Met modified Rome II criteria for CC
  – Had <3 CSBM/week
  – ≤6 SBMs per week during a 2-week baseline period

• Treatments
  – Oral once-daily 133 or 266μg linaclotide or placebo for 12 weeks
### Results

SBM and CSBM bar figure on single slide put numbers on bar; rest on side following

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>133μg Linaclotide</th>
<th>266μg Linaclotide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MD-01 (n=215)</td>
<td>103-303 (n=209)</td>
<td>MD-01 (n=213)</td>
</tr>
<tr>
<td>SBM Rate</td>
<td>1.187</td>
<td>1.113</td>
<td>4.092***</td>
</tr>
<tr>
<td>CSBM Rate</td>
<td>0.450</td>
<td>0.245</td>
<td>1.942***</td>
</tr>
<tr>
<td>Stool Consistency(1)</td>
<td>0.378</td>
<td>0.331</td>
<td>1.785***</td>
</tr>
<tr>
<td>Straining(2)</td>
<td>-0.378</td>
<td>-0.283</td>
<td>-1.044***</td>
</tr>
<tr>
<td>Abdominal Discomfort(3)</td>
<td>-0.081</td>
<td>-0.132</td>
<td>-0.265**</td>
</tr>
<tr>
<td>Bloating(3)</td>
<td>-0.140</td>
<td>-0.126</td>
<td>-0.311*</td>
</tr>
<tr>
<td>Constipation Severity(3)</td>
<td>-0.130</td>
<td>-0.224</td>
<td>-0.779***</td>
</tr>
</tbody>
</table>

ANCOVA pairwise comparison versus placebo *P<.01, **P<.001, ***P<.0001

1) 7-pt scale (BSFS): 1=separate hard lumps like nuts, 7=watery, no solid pieces
2) 5-pt scale: 1=none, 5=an extreme amount (3) 5-pt scale: 1=none, 5=very severe
Key Takeaway

• Once daily doses of linaclotide resulted in early and sustained statistically significant improvements in bowel and abdominal symptoms during treatment of patients with CC
The *Methanobrevibacter smithii* Concentration in Stool of Subjects with Constipation Predominant IBS is Directly Correlated with Methane on Lactulose Breath Test (P756)
Purpose

• To assess the proportionality between stool *Methanobrevibacter smithii* and methane production on breath test
Methods

• Patients
  – Consecutive Rome II IBS subjects presenting for lactulose breath test
  – Subjects considered methane positive if their methane was >3 ppm at any point during 180 minutes of testing

• Design
  – After completion of breath test, subjects were asked to provide a stool sample that was fresh frozen
  – PCR from stool samples were tested with primers for the *M. smithii* 16S rRNA gene
  – Quantity of *M. smithii* compared to the amount of methane on breath testing using Spearman rank correlation.
Results

- 9 subjects with and 10 without methane completed study
- The C-D was $5.1 \pm 3.8$ compared to $-0.11 \pm 3.6$ for non-methane subjects ($P < 0.01$) indicating greater constipation in methane subjects
- Stool *M. smithii* level:
  - $2.88 \times 10^4$ cfu/mL in non-methane positive subjects
  - $1.47 \times 10^6$ cfu/mL in methane-positive subjects ($P = 0.055$)
- Among methane producing subjects, the amount of methane was significantly correlated with the amount of *M. smithii* in the stool ($R = 0.72$).
Key Takeaway

• Since the amount of methane detected by breath testing appears proportional to the quantity of *Methanobrevibacter smithii* in stool, it is likely that methane on breath test is mostly attributable to this organism
Increased Risk for IGE Among Those with IBS (P1165)
Purpose

- Examined the risk of acute gastroenteritis (AGE) in subjects with existing IBS utilizing data from the US Department of Defense medical encounter data repository
Methods

- Military members with incident IBS were identified and matched with 2 controls
- Medical encounter history analyzed for incident episodes of IGE from documented medical encounters and by self-report
- Incidence rate ratios were used to assess the relationship between IBS and AGE and to control for important covariates
Results

- Identified 9341 incident IBS cases
  - Matched to 18,833 non-IBS subjects
- ~2-fold increase in the risk of developing IBS using the PDHA tool ($P<.01$)
  - Effect was even more pronounced when limited to those that sought care for AGE (RR 2.5, $P<.0001$)
- ~3-fold increased risk ($P<.0001$) of AGE in patients with IBS
Key Takeaways

• Subjects with IBS have an increased risk of AGE for unclear reasons
The Responsiveness and Validity of a Binary Weekly Recall Question and the Proposed FDA Composite Endpoint as Measures of Daily Symptom Severity in Non-Constipation (P770)
Purpose

• Weekly adequate relief of global IBS symptoms and bloating binary endpoints and the FDA composite endpoint using daily assessments were evaluated for responsiveness and validity in 2 identically-designed phase 3, double-blind, placebo-controlled trials
Methods

• Patients
  – Mild to moderate non-constipation IBS (TARGET 1, n=623; TARGET 2, n=637)

• Treatments
  – Rifaximin 550 mg TID or placebo for 2 weeks and evaluated for 10 weeks post treatment

• End points
  – Weekly adequate relief of global IBS symptoms and IBS-related bloating (Yes/No)
  – Daily IBS symptom severity for global IBS symptoms, IBS-related bloating, IBS-related abdominal pain using a 7-point scale
  – Stool consistency using a 5-point scale
  – Per FDA draft guidance, abdominal pain and stool consistency weekly responders were patients who reported ≥ 30% decrease from baseline in abdominal pain and had an average stool consistency score < 4
Results

• Weekly responder endpoints demonstrated responsiveness by consistently correlating with daily symptom severity scores
• Responders had significantly greater improvements in all daily symptom severity scores than non-responders at each week during the course of the study ($P<.0001$)
• Evidence for convergent validity, based on a Spearman’s correlation of 0.40 or greater, was observed for weekly responders with daily symptom severity scores
Key Takeaway

- Both the binary weekly adequate relief as well as the newly proposed FDA composite endpoint are valid and responsive
Rifaximin Treatment Consistently Demonstrated Relief Across Daily Symptoms in Patients with Non-Constipation Irritable Bowel Syndrome: Results from 2 Phase 3 Trials (TARGET 1 and TARGET 2) (55)
Purpose

• Examine effects of rifaximin in patients with non-constipation IBS
Methods

• Patients
  – Mild to moderate non-constipation IBS (TARGET 1, n=623; TARGET 2, n=637)

• Treatment
  – Rifaximin 550 mg TID or placebo for 2 weeks and followed for 10 weeks after treatment

• Primary efficacy endpoint was the proportion of subjects who achieved adequate relief of global IBS symptoms (Yes/No) for ≥2 of 4 weeks during the PEP
  – Adequate relief of bloating, a key secondary endpoint, was similarly evaluated
## Results

### Efficacy Outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global-IBS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly TARGET 1</td>
<td>1.53</td>
<td>(1.10, 2.12)</td>
<td>0.0125</td>
</tr>
<tr>
<td>TARGET 2</td>
<td>1.45</td>
<td>(1.05, 2.01)</td>
<td>0.0263</td>
</tr>
<tr>
<td>Combined</td>
<td>1.49</td>
<td>(1.18, 1.88)</td>
<td>0.0008</td>
</tr>
<tr>
<td><strong>IBS Bloating</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly TARGET 1</td>
<td>1.62</td>
<td>(1.16, 2.27)</td>
<td>0.0045</td>
</tr>
<tr>
<td>TARGET 2</td>
<td>1.49</td>
<td>(1.08, 2.06)</td>
<td>0.0167</td>
</tr>
<tr>
<td>Combined</td>
<td>1.56</td>
<td>(1.23, 1.96)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

### Key Endpoint

- **Odds Ratio and 95% CI**
- Favors Placebo
- Favors *Rifaximin*
## Results

### 2° Endpoints

<table>
<thead>
<tr>
<th>FDA Guidance</th>
<th>Endpoint</th>
<th>TARGET 1</th>
<th>TARGET 2</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global-IBS Daily</td>
<td>TARGET 1</td>
<td>1.76</td>
<td>1.59</td>
<td>1.61</td>
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<tr>
<td></td>
<td>TARGET 2</td>
<td>(1.26,2.47)</td>
<td>(1.13,2.24)</td>
<td>(1.28,2.04)</td>
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<tr>
<td></td>
<td>Combined</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
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<tr>
<td>IBS Bloating Daily</td>
<td>TARGET 1</td>
<td>1.41</td>
<td>1.76</td>
<td>1.52</td>
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<tr>
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<td>TARGET 2</td>
<td>(1.00,1.97)</td>
<td>(1.26,2.44)</td>
<td>(1.21,1.62)</td>
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<td>IBS Ab Pain Daily</td>
<td>TARGET 1</td>
<td>1.45</td>
<td>1.46</td>
<td>1.42</td>
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<tr>
<td></td>
<td>TARGET 2</td>
<td>(1.05,2.02)</td>
<td>(1.05,2.03)</td>
<td>(1.13,1.78)</td>
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<tr>
<td></td>
<td>Combined</td>
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<td>0.0028</td>
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<tr>
<td>Ab Pain &amp; Stool Daily</td>
<td>TARGET 1</td>
<td>1.40</td>
<td>1.55</td>
<td>1.47</td>
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<td></td>
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<td>(1.02,1.92)</td>
<td>(1.12,2.13)</td>
<td>(1.17,1.84)</td>
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<tr>
<td></td>
<td>Combined</td>
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<td>0.0009</td>
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Key Takeaways

- Rifaximin 550 mg TID taken for 2 weeks provided consistent and statistically significant relief of IBS symptoms during the 4 weeks following treatment in 2 separate phase 3 trials