Managing Chronic Constipation and IBS with Constipation
New Evidence of Overlap, Distinctions, and Improved Treatment Strategies

Agenda

• Welcome and Introductions
• Incidence and Impact of CC and IBS-C
• CC and IBS-C: 1 Disease or 2?
• Individualized Treatment of Patients with CC and IBS-C
  – Young Woman with Constipation and Abdominal Discomfort
  – Older Man with Constipation
• Key Points and Faculty Q & A

CC, chronic constipation; IBS-C, irritable bowel syndrome with constipation
INCIDENCE AND IMPACT OF IBS-C AND CC

### Impact of IBS

<table>
<thead>
<tr>
<th>Prevalence(^1)</th>
<th>Direct Costs(^2-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 10%–15% of US population</td>
<td>• Up to 12% of all PCP visits(^3); ≤ 3.5 million physician visits/y(^4)</td>
</tr>
<tr>
<td></td>
<td>• 50% higher costs vs matched controls(^2)</td>
</tr>
<tr>
<td></td>
<td>– 3x more likely to undergo cholecystectomy</td>
</tr>
<tr>
<td></td>
<td>– 25% of colonoscopies in patients &lt; 50 y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Demographics(^1,2)</th>
<th>Indirect Costs(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All ages; mostly &lt; 50 y</td>
<td>• 3%–5% Absenteeism</td>
</tr>
<tr>
<td>• 3:1 female : male</td>
<td>• 26%–31% Presenteeism (impaired productivity)</td>
</tr>
<tr>
<td>• Non-whites &gt; whites</td>
<td></td>
</tr>
</tbody>
</table>

### HRQOL Impact\(^2,5\)

<table>
<thead>
<tr>
<th>(</th>
<th>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SF-36 scores lower than for other chronic illnesses</td>
<td></td>
</tr>
<tr>
<td>• Impact as significant as heart failure and dialysis-dependent kidney failure</td>
<td></td>
</tr>
</tbody>
</table>

*varies based on diagnostic criteria used; HRQOL, health-related quality of life; SF-36, Short Form Health Survey


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# Managing Chronic Constipation and IBS with Constipation

New Evidence of Overlap, Distinctions, and Improved Treatment Strategies

## Impact of CC

<table>
<thead>
<tr>
<th>Prevalence¹</th>
<th>Direct Costs²,³</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≤ 20% of North American population</td>
<td>• ≈ 2 million patients/y visit a doctor (2004)²</td>
</tr>
<tr>
<td></td>
<td>• 48,450 patients/y hospitalized (2010)³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Demographics¹</th>
<th>Indirect Costs⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All ages; prevalence increases ≥ 65 y</td>
<td>• 13.7 million days restricted activity/y</td>
</tr>
<tr>
<td>• ≈ 2 : 1 Female &gt; male</td>
<td></td>
</tr>
</tbody>
</table>

**HRQOL Impact¹,⁵**

• Significantly lower SF-36 scores vs healthy controls

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## Patient Case 1

**Young Woman with Constipation and Abdominal Discomfort**
Patient Case 1
19 y/o female with constipation and abdominal discomfort

- 19-year-old female presents to the student health service c/o chronic infrequent hard stools (2-3 stools/wk) for 3 to 4 mo. She reports increasing abdominal discomfort (bloating) and pain during past few weeks. The pain improves with defecation, which often requires use of an enema and/or laxative
- Social history
  - Sophomore in college living in student housing with full academic scholarship
- Past medical history
  - Negative
- Treatment course
  - Referred for primary care follow-up
  - Told to increase fiber and fluid in her diet

Rome III Diagnostic Criteria for IBS*

- Recurrent abdominal pain or discomfort at least 3 d/mo in the last 3 mo associated with ≥2 of the following:
  - Improvement with defecation
  - Onset associated with a change in frequency of stool
  - Onset associated with a change in form of stool

*Criteria fulfilled for the last 3 mo with symptom onset at least 6 mo prior to diagnosis
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Definitions of IBS: Bristol Stool Form Scale

- Chronic, recurrent abdominal pain or discomfort not explained by structural or biochemical abnormalities

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
<th>Type 4</th>
<th>Type 5</th>
<th>Type 6</th>
<th>Type 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Separate hard lumps, like nuts (hard to pass)</td>
<td>Sausage-shaped but lumpy</td>
<td>Like a sausage but with cracks on its surface</td>
<td>Like a sausage or snake, smooth and soft</td>
<td>Soft blobs with clear-cut edges (passed easily)</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
<td>Watery, no solid pieces, entirely liquid</td>
</tr>
</tbody>
</table>

IBS-C
Hard/lumpy stools ≥25%
Loose/watery stools <25%

IBS-M
Hard/lumpy stools ≥25%
Loose/watery stools ≥25%

IBS-D
Hard/lumpy stools <25%
Loose/watery stools ≥25%

Rome III Diagnostic Criteria for CC

- Symptoms insufficient to satisfy IBS criteria
- ≥2 of the following
  - During ≥25% of defecations
    - Straining
    - Lumpy or hard stools
    - Sensation of incomplete evacuation
    - Facilitation by manual maneuvers
  - <3 defecations/wk
- Loose stools rarely present without laxative use

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IBS-C AND CC: 1 DISEASE OR 2?

Discriminating Between IBS-C and CC is Challenging

- Limitations of the Rome III criteria$^{1,2}$
  - IBS grouped into subtypes based on the predominant stool consistency
  - By definition, all patients with IBS have abdominal pain or discomfort
  - Abdominal pain/discomfort are not included in the definition for CC

- Clinical challenges$^{1,2}$
  - IBS-C and CC share symptoms such as bloating (hard to differentiate from discomfort)
  - IBS-C patients may have only mild pain; CC patients sometimes have “some” pain
  - The same treatments (including new laxatives and prokinetics) may successfully treat both conditions

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Overlap of IBS-C and CC
Rome III Diagnostic Criteria

IBS-C (n = 201)  CC (n = 411)

- IBS-C patients had significantly greater frequency of abdominal pain/discomfort
  - Yet, 44.8% of CC patients reported experiencing abdominal pain/discomfort within past 3 mo
- IBS-C symptoms more severe
  - May represent different ends of spectrum of same condition

The Overlap of IBS-C and CC

- Some patients with CC have abdominal pain and discomfort without fulfilling IBS criteria
- Phone survey of random sample of Spanish population (n=1500 valid interviews)
  - Overall prevalence of CC: 19.2%
    - 13.9% for nonpainful CC
    - 2.0% for painful CC
    - 3.3% for CC in patients with IBS
  - CC more prevalent
    - Among women (ratio of 2.7:1)
    - With increasing age
  - CC prevalence inversely related to liquid intake and physical activity (P<.01; χ² -test)
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Bowel Symptoms in Patients with CC and IBS-C

IBS-C and CC may Represent a Spectrum of Visceral Sensitivity Modulated by Serotonin

- Study in individuals with IBS-C (n=23), FC (n=11), controls (n=23)
- Patients with IBS-C or FC had similar
  - Baseline symptoms and bowel habits
  - Colonic transit and response to meal ingestion
  - Fasting concentrations of serotonin
- IBS-C: increased symptoms after meal ingestion (P<.001) and lower sensory thresholds
- Serotonin correlated inversely with defecation frequency (IBS-C or FC) (P=.03)
- Serotonin correlated with pain threshold (P=.02) and stool threshold (P=.06)
- Conclusions
  - FC and IBS-C, based on Rome III criteria, are not distinct disorders, symptomatically or physiologically
  - They appear to lie in a spectrum of visceral sensitivity modulated by serotonin signaling

FC, functional constipation
Overlap of IBS-C and CC

**Current Knowledge**
- In CC, symptoms of abdominal pain/discomfort not included in the definition, but some patients with CC have abdominal pain/discomfort without fulfilling criteria for IBS

**New Insights**
- Subjects with painful CC and CC with IBS younger, reported more constipation, had more symptoms than subjects with nonpainful CC
- CC associated with age and physical activity
- CC appears to be a spectrum: most patients do not have abdominal pain/discomfort, but others (with otherwise quite similar characteristics) are patients with IBS or fall outside any established diagnosis


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**Patient Case 1**
Management of IBS-C: Self-treatment with Laxatives
Patient Case 1 (continued)

19 y/o female with constipation and abdominal discomfort

• Treatment course
  – At a follow-up visit at student health clinic 2 mo later, patient reports compliance with increased fiber and fluids with only slight improvement in symptoms
  – She is still using OTC laxatives frequently

Myths and Misconceptions: Chronic Laxative Use and Other Treatments for Constipation

• Fiber intake: patients with more severe constipation may get worse
• Fluid intake: no evidence of efficacy for constipation unless evidence of dehydration
• Stimulant laxatives\(^1,2\)
  – No convincing evidence that chronic use causes structural or functional impairment of enteric nerves or intestinal smooth muscle
  – No reliable data to link chronic use of stimulant laxatives to colorectal cancer and other tumors
  – Some patients with CC are dependent on laxatives to achieve satisfactory bowel function, but this is not the result of prior laxative intake
  – Tolerance to stimulant laxatives is uncommon
  – No evidence for occurrence of “rebound constipation” after stopping laxative intake
  – While laxatives may be misused, no potential for addiction

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OTC, over-the-counter


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Bisacodyl Effective and Safe for CC

4-Week Study of Bisacodyl 10 mg qd or Placebo

<table>
<thead>
<tr>
<th></th>
<th>Baseline (N=368)</th>
<th>Placebo (n=121)</th>
<th>Bisacodyl (n=247)</th>
<th>Adjusted Mean Improvement From Baseline in PAC-QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Mean # CSBMs/wk</td>
<td>1.1</td>
<td>1.9</td>
<td>5.2</td>
<td>• Worries and concerns</td>
</tr>
<tr>
<td>Increase ≥1 in Mean # CSBMs/wk</td>
<td>—</td>
<td>40.2%</td>
<td>82.0%</td>
<td>• Physical discomfort</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Satisfaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Overall score</td>
</tr>
</tbody>
</table>

CSBM, complete spontaneous bowel movement

Patient Case 1
Management of IBS-C: Diagnostic Workup and Red Flags
Patient Case 1 (continued)
19 y/o female with constipation and abdominal discomfort

• Treatment course
  – Referred for GI consult
  – Prescribed polyethylene glycol 3350 (PEG), 17 g (1 capful) daily as needed for BM

Initial Diagnostic Evaluation for IBS

• Patient history\textsuperscript{1,2}
  – Symptom severity / duration
  – Family history
  – Psychosocial factors

• No alarm symptoms or “red flags”\textsuperscript{1,2}
• Rome III diagnostic criteria\textsuperscript{2}

AND

• Initial screening tests in some cases based on history\textsuperscript{1}
  – Complete blood count
  – Stool hemoccult

• Further work up only if clinical evidence suggests organic disease\textsuperscript{1,3}
  – Laboratory tests (ie, sedimentation rate, serum chemistry, thyroid function, stool ova, and parasites)
  – Colonoscopy or sigmoidoscopy

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Differential Diagnosis of IBS

Gastrointestinal
- Colorectal neoplasm
- Diverticular disease
- Inflammatory bowel disease
- Malabsorption syndromes

Gynecologic
- Pelvic floor dysfunction
- Endometriosis

Surgical
- Abdominal/pelvic
- Anorectal surgery

Medications
- Opiates
- Antidepressants
- Anticholinergics
- Laxatives

Metabolic/Endocrine
- Thyroid dysfunction
- Hypercalcemia
- Hypomagnesemia
- Diabetes

Psychological
- Depression
- Anxiety
- Somatization disorder

Systemic
- Amyloidosis
- Scleroderma
- Polymyositis

Neurologic
- Parkinson’s
- Multiple sclerosis
- Autonomic neuropathy

Differential Diagnosis

Red Flags for Organic GI Conditions Requiring Further Work-up

- **History**
  - Unintentional weight loss (>10% IBW)
  - Onset in older patient (>50 y)
  - Family history of GI malignancy or IBD/celiac disease
  - Rectal/GI bleeding
  - Recurrent nausea and vomiting

- **Physical Exam**
  - Rectal bleeding obstructions
  - Positive FOBT
  - Flexible sigmoidoscopy or colonoscopy

- **Laboratory Tests**
  - ↓ Hb
  - ↑ WBC
  - ↑ CRP
  - Abnormal chemistry
  - Abnormal TSH

CRP, C-reactive protein; FOBT, fecal occult blood test; Hb, hemoglobin; IBD, irritable bowel disease; IBW, ideal body weight; TSH, thyroid stimulating hormone; WBC, white blood cells


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Patient Case 1
Management of IBS-C: Pathophysiology and Correlation with Treatment

Patient Case 1 (continued)
19 y/o female with constipation and abdominal discomfort

• Treatment course
  – At GI follow-up 3 mo later, she notes increased frequency of soft stools, sometimes diarrhea
  – She also says she is currently studying for final exams, and her abdominal pain is worse in the last few days
  – Also complains of frequent nausea since starting PEG
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New Evidence of Overlap, Distinctions, and Improved Treatment Strategies

Biopsychosocial Model of IBS Pathophysiology

Early learning
Family influences

External Stressor
- Adverse life events
- Chronic psychological stress
- Gastrointestinal infection
- Changes in diet

Psychological disturbance
Physiologic disturbance

Susceptible individual

Genes

IBS symptoms

Biopsychosocial Model of IBS Pathophysiology

Stress Leads to Disruption of the Brain-Gut-Microbiota Axis in IBS

Stress

Visceral hypersensitivity
Endocrine functions
Neurotransmitters/peptides
Immune function/cytokines
Motility
Microbiota

Patient Case 1
Management of IBS-C: Individualizing Treatment

Model for Individualized Multidisciplinary Treatment of IBS

- Psychological treatments
- Continuing care
- Improve functioning

+ • Follow-up visit
  • Manage stress
  • Pharmacotherapy

+ • Diet, lifestyle, advice
  • Positive diagnosis
  • Explain, reassure
Patient Case 1 (continued)

19 y/o female with constipation and abdominal discomfort

- Treatment course
  - Started on linaclotide 290 μg qd
  - Referred for CBT and stress management
  - Reports “trouble sleeping”
  - At follow-up 4 wk later, she reports improvement in constipation but still having abdominal pain and bloating

Overview of Psychological Treatments of IBS

Treatments Show Greater Efficacy than Usual Care

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>No. of Studies</th>
<th>N</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients</td>
</tr>
<tr>
<td>CBT</td>
<td>7</td>
<td>279</td>
<td>212</td>
</tr>
<tr>
<td>Hypnotherapy</td>
<td>2</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Multicomponent psychological therapy</td>
<td>4</td>
<td>106</td>
<td>105</td>
</tr>
<tr>
<td>Stress management</td>
<td>1</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Dynamic psychotherapy</td>
<td>2</td>
<td>138</td>
<td>135</td>
</tr>
</tbody>
</table>

RR, relative risk; CI, confidence interval
### Antidepressants for IBS

<table>
<thead>
<tr>
<th>Class</th>
<th>Advantages</th>
<th>Concerns</th>
<th>Therapeutic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs</td>
<td>• Best studied class</td>
<td>• AEs: constipation, tachycardia, urinary retention, insomnia, agitation, nightmares</td>
<td>• IBS patients with persistent, moderate to severe symptoms predominated by abdominal pain and loose stools</td>
</tr>
<tr>
<td></td>
<td>• ACG review (9 RCTs, N=575): NNT=4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Relieved global symptoms and abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>• ACG review (5 RCTs, N=230): Superiority vs placebo, NNT=3.5</td>
<td>• Limited data on safety and tolerability</td>
<td>• Patients who can’t tolerate AEs of TCAs</td>
</tr>
<tr>
<td></td>
<td>• Relieved global symptoms and abdominal pain</td>
<td></td>
<td>• May increase intestinal transit and be better suited for patients with IBS-C and concomitant anxiety disorders</td>
</tr>
</tbody>
</table>

ACG, American College of Gastroenterology; AE, adverse event; NNT, number needed to treat; RCT, randomized controlled trial

### Antidepressants for IBS (continued)

<table>
<thead>
<tr>
<th>Class</th>
<th>Advantages</th>
<th>Concerns</th>
<th>Therapeutic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRIs</td>
<td>• Duloxetine evaluated in 1 small study (N=15)</td>
<td>50% drop-out rate due to AEs with duloxetine</td>
<td>Pending results of large, well-designed RCTs</td>
</tr>
<tr>
<td></td>
<td>– Significant improvement in abdominal pain, loose stools, QOL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Venlafaxine shown to increase colonic compliance, colonic tone and decrease sensations of colonic distention</td>
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</tr>
</tbody>
</table>

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“Ideal” Office Visit for IBS Provides Accepting and Supportive Environment


Patient Case 1
Management of IBS-C: Symptom-driven Management
Managing Chronic Constipation and IBS with Constipation

New Evidence of Overlap, Distinctions, and Improved Treatment Strategies

### Symptom-Driven Treatment Choices for IBS

![Symptom-Driven Treatment Choices for IBS Diagram]


### ACG IBS Task Force Evidence-Based Summary: IBS Therapies

<table>
<thead>
<tr>
<th></th>
<th>Global Symptoms</th>
<th>Pain</th>
<th>Bloating</th>
<th>Stool Frequency</th>
<th>Stool Consistency</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber (psyllium)</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>2C</td>
</tr>
<tr>
<td>Laxatives (PEG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>2C</td>
</tr>
<tr>
<td>Lubiprostone</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>1B</td>
</tr>
<tr>
<td>Linaclotide*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1A</td>
</tr>
</tbody>
</table>

*Linaclotide was not approved at the time of the 2009 ACG Task Force publication; this rating reflects consensus of this faculty panel.*

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Lubiprostone for IBS-C: Combined Data from 2 Phase 3 Trials

- 12-wk treatment period
- Monthly responder: at least moderate relief 2-4 wk or significant relief >2-4 wk
- Overall responder: monthly responder ≥2-3 mo

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Chloride Channels in Intestinal Transport
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Linaclotide MOA to Reduce Chronic Abdominal Pain in IBS-C

- Activates GC-C expressed on mucosal epithelial cells, resulting in production and release of cGMP
- Extracellular cGMP acts on and inhibits nociceptors

Linaclotide Phase 3 Studies in IBS-C

EMA Analysis

$\geq 6/12$ wk considerable or complete relief of IBS symptoms

<table>
<thead>
<tr>
<th></th>
<th>12-wk responder $\Delta$</th>
<th>12-wk responder $\Delta$</th>
<th>26-wk responder $\Delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>15.6%</td>
<td>21.1%</td>
</tr>
<tr>
<td>12-wk responder</td>
<td></td>
<td>33.8*</td>
<td>36.7*</td>
</tr>
<tr>
<td>Placebo</td>
<td>18.2</td>
<td>15.6</td>
<td>14.1</td>
</tr>
<tr>
<td>Linaclotide</td>
<td>395</td>
<td>405</td>
<td>403</td>
</tr>
<tr>
<td>Trial 31</td>
<td>401</td>
<td>401</td>
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</tbody>
</table>

$P<.0001$
EMA, European Medicines Agency
Managing Chronic Constipation and IBS with Constipation
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Linaclotide Phase 3 IBS-C Trial
SBMs and CSBMs Over 26 Wk

Treatment Groups
- 266 µg
- Placebo

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Meta-analysis of Linaclotide for IBS-C

A. FDA Responder
Improvement of ≥30% from baseline in average daily worst abdominal pain + increase of ≥1 CSBM from baseline for 50% of weeks

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Linaclotide</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chey</td>
<td>135</td>
<td>401</td>
<td>2.42 [1.83, 3.20]</td>
<td></td>
</tr>
<tr>
<td>Rao</td>
<td>136</td>
<td>405</td>
<td>1.60 [1.26, 2.02]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>271</td>
<td>798</td>
<td>1.95 [1.30, 2.94]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>806</td>
<td>395</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2 = 0.07$, $\chi^2 = 5.02$, df = 1 ($p = 0.03$); $I^2 = 80%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 3.21$ ($p = 0.001$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. Abdominal Pain Responder
≥30% decrease in worst abdominal pain for 75% of weeks

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Linaclotide</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chey</td>
<td>156</td>
<td>403</td>
<td>1.98 [1.57, 2.50]</td>
<td></td>
</tr>
<tr>
<td>Rao</td>
<td>139</td>
<td>405</td>
<td>1.27 [1.03, 1.56]</td>
<td></td>
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<tr>
<td>Total (95% CI)</td>
<td>295</td>
<td>798</td>
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<td>Total events</td>
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<td></td>
<td></td>
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<tr>
<td>Heterogeneity: $\tau^2 = 0.09$, $\chi^2 = 7.88$, df = 1 ($p = 0.005$); $I^2 = 87%$</td>
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<td>Test for overall effect: $Z = 2.04$ ($p = 0.04$)</td>
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Patient Case 1
Management of IBS-C: AEs

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Most Common AEs in Clinical Trials

- **Lubiprostone 24 μg bid\(^1\)**
  - Nausea (31.1%)
  - Diarrhea (13.2%)
  - Headache (13.2%)
  - Abdominal pain (6.7%)

- **Linaclotide 290 μg qd\(^2\)**
  - Diarrhea (18%)
  - Nausea (4%)
  - Abdominal pain (4%)


Safety Summary of Novel Agents for IBS-C

- Most reported AEs of mild-to-moderate severity, related to GI tract
- Lubiprostone and linaclotide have low systemic bioavailability and fewer AEs
- Diarrhea significantly higher with linaclotide than placebo
- Lubiprostone may rarely cause dyspnea
- Lubiprostone and linaclotide cause dose-dependent AEs; starting treatment with lowest effective doses recommended

KEY TAKEAWAYS: IBS-C

- IBS-C can be differentiated from CC by the presence of persistent abdominal pain and discomfort
- Management of IBS-C should be individualized and targeted to the multifactorial pathophysiology and specific patient symptoms
- Newer treatment options (linaclotide, lubiprostone) address multifactorial symptoms including abdominal pain
- Psychosocial interventions and establishing a therapeutic patient relationship are important

Patient Case 2
Focus on Management of CC
Patient Case 2
65 y/o male with constipation

• Presents with difficulty evacuating his bowels
  – Without laxatives, has 1 BM every 3-4 d with straining; often requires digitalization
  – Spends ≥30 m attempting to evacuate bowels
  – Supplemental fiber and OTC laxatives worsen symptoms (crampy abdominal pain)

• Medical history
  – Osteoarthritis, hypertension, gout

• Medications
  – Multivitamin + iron daily
  – Daily fiber supplement
  – NSAID agents daily for pain
  – Calcium channel blocker
  – Colchicine prn

Patient Case 2 (continued)
65 y/o male with constipation

• Pertinent history and physical exam
  • Denies rectal bleeding, fever, weight loss
  • No palpable abdominal/rectal mass
  • Digital exam showed normal resting tone with a paradoxical contraction of the anal sphincter when simulating defecation
  • Stool guaiac negative
Rome III Diagnostic Criteria for CC

- Symptoms insufficient to satisfy IBS criteria
- ≥2 of the following
  - During ≥25% of defecations
    - Straining
    - Lumpy or hard stools
    - Sensation of incomplete evacuation
    - Facilitation by manual maneuvers (digitalization, support of pelvic floor)
  - <3 defecations/wk
- Loose stools rarely present without laxative use


Pathophysiology of CC

Primary subtypes of constipation

Normal-transit constipation
Defecatory dysfunction
- Inability to coordinate muscles
- Can overlap with STC
- Dyssynergic defecation
  - Megarectum
  - Rectocele
  - Perineal descent

Slow-transit constipation (STC)
- Decreased colonic motility
- Blunted response to meals
- Absent pacemaker cells

STC, slow transit constipation
Managing Chronic Constipation and IBS with Constipation
New Evidence of Overlap, Distinctions, and Improved Treatment Strategies

The Burden of CC on QOL

Patient Case 2
Management of CC: Secondary Causes of Constipation

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Anatomy and Physiology of the Pelvic Floor

**Normal Defecation**
- Sensory perception of stool
- Rectal distension
- Contract diaphragm, abdomen, rectal muscles
- Relax external anal sphincter (decreased sphincter pressure)
- Relax puborectalis muscle

**Dyssynergic Defecation**
- Prolonged colonic transit time
- Discoordination of abdominal, rectoanl, and pelvic floor muscles
- Rectal hyposensitivity
- Paradoxical increase in sphincter pressure
- <20% relaxation of resting anal sphincter pressure
- Inadequate abdomino-rectal propulsive forces

This information was originally published in Andrews CN et al. Canadian Journal of Gastroenterology. 2011;25(SB):16B-21B.

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Digital Exam: Normal Anorectal Physiology

**At Rest**
- Anorectal Angle ~90°

**During Straining**
- Angle more obtuse
- Sphincter relaxes
- Pelvic floor descends

Illustrations © The Rome Foundation.
Secondary Causes of Constipation

- **Endocrine/metabolic**
  - Diabetes / thyroid / hypercalcemia
- **Neurologic**
  - Spinal cord / MS / Parkinson’s / Hirschsprung’s disease
- **Anorectal**
  - Anal fissures, strictures / IBD / rectocele / CRC
- **Psychogenic**
  - Depression / eating disorders
- **Iatrogenic**
  - Medications / surgery
- **Enteric myopathy / neuropathy**
  - Scleroderma / amyloidosis

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Secondary Causes of Constipation

CRC, colorectal cancer; MS, multiple sclerosis

Medications That May Contribute to CC

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- Sympathomimetics
- Antipsychotics
- Diuretics
- Antihistamines

Medications That May Contribute to CC

NSAIDs, nonsteroidal anti-inflammatory drugs

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Managing Chronic Constipation and IBS with Constipation
New Evidence of Overlap, Distinctions, and Improved Treatment Strategies

Alarm Features Requiring Further Workup in CC

- Unremitting or nocturnal symptoms
- Palpable abdominal/rectal mass
- Family history of organic GI disease
- Anemia or iron deficiency
- Rectal bleeding, fever, weight loss
- Severe symptoms not investigated
- Symptom onset at >50 y old; >45 y if African-American


Patient Case 2
Management of CC: Evidence-based Treatment

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Managing Chronic Constipation and IBS with Constipation
New Evidence of Overlap, Distinctions, and Improved Treatment Strategies

**CC Management Pyramid**

1. **Surgery**
2. **Linaclotide**
3. **Lubiprostone**
4. **Osmotic laxative**
5. **Fiber supplement**
6. **Eliminate modifiable factors**
7. **Counsel on diet and physical activity**
8. **Education**
9. **Acknowledge and address patient concerns**
10. **Set realistic expectations and encourage patient participation**

Liu LWC. Am J Gastroenterol. 2011;25(Suppl B):22B-28B.

**CC Management Approach**

1. Patient with infrequent and/or hard stool and/or difficult to pass stools when not on laxatives
2. History and physical exam
3. Alarm features?
   - yes
   - no
4. Investigations as indicated, eg. colonoscopy, metabolic screen
5. Any abnormality identified?
   - yes
   - no
6. Colorectal cancer or other obstructing lesion, anorectal disease, hypothyroidism, hypercalcemia
7. Constipating drugs
   - yes
   - no
8. Stop drugs where possible
9. Symptom improvement?
   - yes
   - no
10. Drug-induced constipation
11. Functional constipation
12. Explanation physiology, modify life style and diet, discuss bulking agents, simple laxatives
13. Symptom improvement?
   - yes
   - no
14. Formulate longer term management plan
15. Refer for consideration of physiological assessment (anorectal function, colonic transit), see 'refractory constipation and difficult defecation' algorithm


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Managing Chronic Constipation and IBS with Constipation
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**Lubiprostone for CC**

- Multicenter parallel group, double-blind controlled trial
- 4-wk treatment period
- Primary endpoint: # SBMs

*P<.001

**Linaclotide for CC: Primary Results from 2 Phase 3 Clinical Trials**

Responder: ≥3 CSBM/wk and increase of ≥1 CSBM/wk for ≥9/12 wks

*P≤.0012

- L 145 μg (n=430)
- L 290 μg (n=418)
- Placebo (n=424)

- Most common AE: diarrhea (14%-16% vs 4.7%)
- Discontinuation (4% vs 0.5%)

Linaclotide for CC: QOL Results from 2 Phase 3 Clinical Trials

Domains of physical discomfort, worries/concern, satisfaction improved on PAC-QOL

**P<.05

Linaclotide for CC: QOL Results from 2 Phase 3 Clinical Trials

% Responders Wk 12

PAC-QOL Overall Score

Trial 303

Trial 01

0 20 40 60

42.2 46.8

44.9 35.5

27.8 18.7

*L* 145 μg (n=430)

L 290 μg (n=418)

Placebo (n=424)

Strength of Recommendations for CC Therapies

<table>
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<tr>
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<th>Level of Recommendation¹</th>
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<td>Psyllium</td>
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<tr>
<td>PEG</td>
<td>A</td>
</tr>
<tr>
<td>Lactulose</td>
<td>A</td>
</tr>
<tr>
<td>Senna</td>
<td>A</td>
</tr>
<tr>
<td>Bisacodyl</td>
<td>A</td>
</tr>
<tr>
<td>Lubiprostone</td>
<td>A</td>
</tr>
<tr>
<td>Linaclotide</td>
<td>A*²</td>
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</tr>
<tr>
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<td>B</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>B</td>
</tr>
<tr>
<td>Docusate sodium</td>
<td>B</td>
</tr>
<tr>
<td>Milk of magnesia</td>
<td>C</td>
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</tbody>
</table>

*Linaclotide not included in this review; level of recommendation provided by faculty panel

Response to Biofeedback for Defecatory Dysfunction

- Patients who failed to respond to fiber 20 g/d randomized to receive 5 weekly biofeedback sessions or PEG 14.6-29.2 g/d plus 5 weekly counselling sessions\(^1\)
- Evaluated for major improvement in constipation and pelvic floor relaxation at 6 mo\(^1\)
- Biofeedback efficacy in patients with pelvic floor dyssynergia persisted for at least 2 y\(^2\)
- Slow transit constipation without dyssynergia is not responsive to psychological treatments\(^2\)


KEY TAKEAWAYS: CC

- Effective management of CC includes identifying and addressing secondary causes
- Effective treatment options include fiber, osmotic laxatives, stool softeners, stimulant laxatives, lubricants, and newer agents (lubiprostone, linaclotide)
Q & A

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