Relieving the burden of Chronic Constipation

Ron Schey, MD.,FACG
Assoc. Director, Neurogastroenterology & Esophageal Disorders Program
Section of Gastroenterology
Lewis Katz School of Medicine Temple University
Constipation in the United States

- **Prevalence**
  - Estimates range between 12-19%
  - More women and non-Caucasians seek care

- **QoL**
  - Lower than the normal population

- **Resource utilization**
  - 13.7 million days per year of restricted activity
  - 2.5 million physician visits annually
  - OTC laxatives: $800 million annually
  - Tertiary care evaluation: average of $2752/patient

Prevalence of Constipation Compared to Other Common Diseases

Prevalence of Selected Diseases in US Adults

- Coronary heart disease: 5.9%
- Asthma: 6.4%
- Diabetes: 6.7%
- Migraines: 15.1%
- Hypertension: 21.6%
- Constipation: 27.2%*

Effects of Constipation on Psychological Profiles

Rao et al Gastroenterology 2005;A123

* = p < 0.05 vs. Slow Transit
† = p < 0.05 vs. Controls
Epidemiology

- Occurs in more women than men
  - Median female/male ratio 2.20

- Increased prevalence associated with
  - Increasing age
  - Depression/psychological distress
  - Lower socioeconomic status
  - Lower education level
  - Lower amount of exercise
  - Non-Caucasian ethnicity

Symptom Overlap and Comorbidities Among GI Motility Disorders

- Diarrhea
- Heartburn
- Regurgitation
- Bloating
- Abdominal pain
- Dyspepsia
- IBS
- Reflux disease
- Constipation
- Pain

Belching
Discomfort

Who Sees Constipation Patients?

- Family Practitioners: 31%
- Internists: 20%
- Gastroenterologists: 4%
- Pediatricians: 15%
- Surgeons: 9%
- OB/GYN: 9%
- Other: 12%

Physician vs Patient’s perception of Constipation

- 418/531 patients in primary care and 57/100 specialists & residents responded

<table>
<thead>
<tr>
<th>Definition</th>
<th>Patients (%)</th>
<th>Physicians (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defecation every 2 days or less frequently</td>
<td>27%</td>
<td>-</td>
</tr>
<tr>
<td>Defecation every ≤3 days</td>
<td>25%</td>
<td>27%</td>
</tr>
<tr>
<td>Defecation every ≤4 days</td>
<td>13%</td>
<td>46%</td>
</tr>
<tr>
<td>Hard Stool alone</td>
<td>25%</td>
<td>6%</td>
</tr>
<tr>
<td>Hard stool + Altered Frequency</td>
<td>10%</td>
<td>21%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

50% of patients used different criteria to physicians

Herz et al. Family Practice 1996
A

Type 1
Separate hard lumps, like nuts (hard to pass)

Type 2
Sausage-shaped but lumpy

Type 3
Like a sausage but with cracks on the surface

Type 4
Like a sausage or snake, smooth and soft

Type 5
Soft blobs with clear-cut edges

Type 6
Fluffy pieces with ragged edges, a mushy stool

Type 7
Watery, no solid pieces, entirely liquid

B

25% of BM is the threshold for classification

% BM hard or lumpy

0 25 50 75 100

% BM loose or watery

IBS-C
IBS-M
IBS-U
IBS-D

Bristol types 1 and 2
Bristol types 1 and 6
Bristol types 6 and 7
Defecation

- Relaxation of the muscular sling created by the puborectalis anorectal angle widens
- Straightening the anorectal canal, EAS is relaxed and the anterior abdominal musculature, diaphragm, and rectum contract, leading to expulsion of the stool via increased intra-abdominal pressure
- After this, the IAS and puborectalis return to their resting contracted state

Rome IV Working Group
Criteria for Chronic Constipation

- Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis with 2 or more of:
  - Straining
  - Lumpy or hard stools
  - Sensation of incomplete evacuation
  - Sensation of anorectal obstruction/blockage
  - Manual maneuvers to facilitate defecation
  - < 3 BMs/week

- Loose stools are not present

- Insufficient criteria for IBS

More than one fourth (25%) of bowel movements with Bristol stool form types 1 or 2 and less than one-fourth (25%) of bowel movements with Bristol stool form types 6 or 7

Alternative for epidemiology or clinical practice: Patient reports that abnormal bowel movements are usually constipation

# IBS-C versus Chronic Constipation

<table>
<thead>
<tr>
<th>Symptoms &gt;3 Months</th>
<th>IBS-C</th>
<th>Chronic Constipation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Straining</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Hard/lumpy stools</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>&lt;3 BMs/wk</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Feeling of incomplete evacuation</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Bloating/abdominal distension</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Abdominal pain/discomfort</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

Alarm Features That May Suggest a Secondary Cause of Constipation

- Hematochezia
- Family history of colon cancer
- Family history of IBD
- Anemia
- Positive fecal occult blood test
- “Unexplained” weight loss ≥ 10 pounds
- Severe, persistent constipation that is unresponsive to treatment (Think carefully)
- New-onset constipation in an elderly patient
Potential Secondary Causes of Constipation

- Pregnancy
- Collagen vascular and muscle disorders
- Central nervous system disorders
- Medications
- Mechanical obstruction
- Metabolic and endocrine disorders
- Neurological disorders

Borum ML. *Prim Care.* 2001
Examples of Medications Associated With Constipation

- **Prescription drugs**
  - Opiates
  - Anticholinergic agents
  - Tricyclic antidepressants
  - Calcium channel blockers
  - Anti-Parkinsonian drugs
  - Sympathomimetics
  - Antipsychotics
  - Diuretics
  - Antihistamines

- **Nonprescription drugs**
  - Antacids, especially calcium-containing
  - Calcium supplements
  - Iron supplements
  - Antidiarrheal agents
  - Nonsteroidal anti-inflammatory agents

Slow transit and IBS-C overlap in half of each group

Schiller LR. Aliment Pharmacol Ther. 2001
24 hr Colonic Manometry Profile

- **Health**
- **Constipation**

Area Under the Curve (mm Hg*s)

**Time**

- 14: Meal
- 16: Sleep
- 18: Waking
- 20: Meal

Rao et al Am J Gastroenterol 2004
Evaluation of Colonic and Anorectal Function

Balloon Expulsion Test

Anorectal manometry

Colonic Transit Study with Sitzmarks

Day 1- One capsule
Day 6 (120 hrs)
- Plain abdomen x-ray
- Normal Transit
  = < 5 markers

FECOM

Colon Transit Scintigraphy

Diagnostic Tests

- Stool diary
- CBC, Electrolytes, Glucose, TSH, Ca
- Colonoscopy (particularly if aged > 50 years)
- Colonic transit studies: radiopaque markers, scintigraphy
- Balloon expulsion tests
- Defecography/MRD
- Anorectal manometry
- Colonic manometry

Basic Clinical Laboratory Tests

- Complete blood count
- Thyroid function tests
  - TSH, free T4
- Measurements of
  - Calcium
  - Electrolytes
- Data do not exist to validate or define the tests that need to be performed
- American College of Gastroenterology task force does not recommend diagnostic testing in patients without alarm signs or symptoms
  - Routine colon cancer screening is recommended for all patients age ≥ 50 years

Digital Rectal Exam

- Place patient in left lateral recumbent position
- Visually inspect the perianal region and perform a digital assessment
  - Squamous cancers and melanoma can occur in anal area
  - External and internal hemorrhoids
  - Anal fissures
  - Resting anal sphincter tone
  - Tone with a squeeze effort
  - Paradoxical pelvic floor contraction with expulsion effort
  - Blood in stool
  - Rectal prolapse
  - Rectocele

Anorectal Manometry

- Rectal Sensors
- Rectum
- Sphincter
- External

(mmHg)
- 140
- 120
- 100
- 80
- 60
- 40
- 20
- 0

10 sec
What is Dyssynergia?

Can Symptoms Predict Dyssynergia?
100 Patients With Difficult Defecation

<table>
<thead>
<tr>
<th>Symptom prevalence</th>
<th>Normal pattern (n = 30)</th>
<th>Dyssynergia (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive straining</td>
<td>92%</td>
<td>89%</td>
</tr>
<tr>
<td>Abdominal fullness</td>
<td>80%</td>
<td>84%</td>
</tr>
<tr>
<td>Incomplete evacuation</td>
<td>72%</td>
<td>95%</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>88%</td>
<td>77%</td>
</tr>
<tr>
<td>Digital maneuvers to defecate</td>
<td>28%</td>
<td>51%</td>
</tr>
</tbody>
</table>

Assessing the colonic microbiome, hydrogenogenic and hydrogenotrophic genes, transit and breath methane in constipation

- 25 healthy and 25 constipated females: evaluated the sigmoid colonic mucosal and fecal microbiota:
  - 16S rRNA gene sequencing
  - abundance of hydrogenogenic FeFe (FeFe-hydA)
  - Methyl coenzyme M reductase A [mrcA] and dissimilatory sulfite reductase A [dsrA]) genes
  - Breath hydrogen and methane levels after oral lactulose
  - Colonic transit with scintigraphy

**Results:** Breath hydrogen and methane were not correlated with constipation, slow colon transit, or with abundance of corresponding genes

After adjusting for colonic transit, gene target in colon mucosa and NOT stool

Wolf PG et al. Neurogastroenterol Motil. 2017
Colonic Transit Study: Subtypes
Colon Transit Scintigraphy

Geometric center (GC)

Opioid induced constipation

New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy that must include 2 or more of the following:

>25% of time

- Straining
- Lumpy or hard stools
- Sensation of incomplete evacuation
- Sensation of anorectal obstruction/blockage
- Manual maneuvers to facilitate defecation
- < 3 BMs/week

- Loose stools are rarely present without use of laxatives
Constipation

- Anti-emetic medications - ondansetron, promethazine, prochlorperazine
- Antihistamines - doxylamine, diphenhydramine, and meclizine

- Iron supplementation formulations
  The degree of constipation is directly proportional to the amount of elemental iron ingested (effect can be mitigated by switching to a formulation containing a lower amount of elemental iron)

- Magnesium sulfate - associated with significant constipation

First-line Approaches to Treating Constipation

- **Lifestyle measures**
  - Increase fluid and dietary fiber intake
  - Exercise
  - Dedicated time to have a BM

- **Fiber supplementation**
  - Begin with 4-6 grams per day
  - Increase gradually as tolerated
  - Recommended intake is 20 to 35 grams per day

- Bran fiber
- Psyllium
- Methylcellulose
- Calcium polycarbophil
- Guar gum

# Common Laxative Classes

<table>
<thead>
<tr>
<th>Laxative</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmotics</td>
<td>Draws water into the bowel from surrounding tissues, softening stool and increasing bowel action. 3 types: saline, lactulose, and polymer.</td>
</tr>
<tr>
<td>Stimulants/Irritants</td>
<td>Acts on the intestinal wall, increasing the muscle contractions that move along stool.</td>
</tr>
<tr>
<td>Lubricants</td>
<td>Coats the bowel and stool mass with a waterproof film, keeping stool soft and easing its passage.</td>
</tr>
<tr>
<td>Combinations</td>
<td>Combinations containing more than 1 type of laxative (ie, a stool softener and a stimulant laxative).</td>
</tr>
</tbody>
</table>
American College of Gastroenterology 2014 Task Force Recommendations

Summary

- Encouraging adequate fluid intake

- Fiber supplements - strong recommendation for use in CIC (20-35 grams/day)

- Laxatives—including polyethylene glycol (PEG8-25 gm/d), lactulose (15-30 cc/d), sodium picosulfate and bisacodyl—have strong recommendations for the treatment of CIC

- Prucalopride, lubiprostone and linaclotide have been given strong recommendations for treatment of CIC

Efficacy of PEG 3350 in Constipation

N = 151 (87% female)

- **PEG 3350**
- **Placebo**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG</td>
<td>2.0</td>
<td>4.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.0</td>
<td>2.9</td>
<td>2.7</td>
</tr>
</tbody>
</table>

- *P < 0.01*
- *P < 0.001*

- Side effects: diarrhea, nausea, abdominal bloating, cramps, and flatulence

Dissatisfaction With Traditional Constipation Treatment Options

Dissatisfaction With Traditional Constipation Treatment Options

Lubiprostone: A Chloride Channel Activator

- Lubiprostone is a gastrointestinal-targeted bicyclic functional fatty acid
- Selectively activates CIC-2 chloride channels, enhancing intestinal fluid secretion
- May restore mucosal barrier function
- Approved by the FDA
  - Treatment of chronic idiopathic constipation in adults
  - IBS-C (women)
  - OIC

Effects of Lubiprostone on Number of Spontaneous Bowel Movements

Effects of Lubiprostone on Number of Spontaneous Bowel Movements

Johanson JF. Gastroenterology 2003

Placebo
24 µg lubiprostone BID

Intent-to-treat population

<table>
<thead>
<tr>
<th>Week</th>
<th>Bowel movements per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Placebo: 3.0</td>
</tr>
<tr>
<td>Week 1</td>
<td>Placebo: 3.0</td>
</tr>
<tr>
<td>Week 2</td>
<td>Placebo: 3.0</td>
</tr>
<tr>
<td>Week 3</td>
<td>Placebo: 3.0</td>
</tr>
<tr>
<td>Week 4</td>
<td>Placebo: 3.0</td>
</tr>
</tbody>
</table>

P = 0.0001  P = 0.0017  P = 0.0002  P = 0.0002

N = 242

Johanson JF. Gastroenterology 2003
Linaclotide

- A 12-Week, Randomized, Controlled Trial With a 4-Week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Linaclotide in Irritable Bowel Syndrome With Constipation

- Reduction of ≥30% in abdominal pain (50.1 vs. 37.5%, \( P=0.0003 \))
- An increase of ≥1 CSBM from baseline (48.6 vs. 29.6%, \( P<0.0001 \))

- Patients remaining on Linaclotide showed sustained improvement

- Diarrhea, the most common AE, resulted in discontinuation of 5.7% of Linaclotide and 0.3% of placebo patients

( caution in children <18 and Elderly)

Plecanatide

- Approved by the FDA for CIC
- Similar to linaclotide, an orally administered, small peptide (16-amino acids) without any apparent systemic absorption
- It activates GC-C receptors, ultimately leading to an increase in intestinal fluid secretion and intestinal motility
- Both dosages of Plecanatide (3 mg 6 mg) resulted in an increase in CSBMs from baseline
- Most common adverse effect: diarrhea (6%)

Naloxegol OIC

- Peripherally acting, $\mu$-opioid receptor antagonist (PAMORA)

- 2 Identical studies significantly higher rate of treatment response, without reducing opioid-mediated analgesia

ITT
Laxative inadequate response

Tenapanor

- New class of medication that is currently under investigation in phase II/III trials with an indication for IBS-C

- Inhibits the Na-H exchanger located on the apical membrane of enterocytes that is responsible for Na and water absorption

- Preliminary study: 50 mg twice daily reportedly statistically improved CSBMs per week

Chey WD, et al. Gastroenterology. 2015
Nerve Stimulation

Percutaneous tibial nerve stimulation:
No benefit to patients with constipation

Sacral nerve Stimulation:
limited efficacy

Graf W. Neurogastroenterol Motil. 2015
Kumar L, et al. Colorectal Dis. 2017
Biofeedback Therapy
Results of Randomized Controlled Trial

- 77 subjects (69 women, mean age 43 years, mean duration 17 years)
- Randomization breakdown:
  - Standard: 24 subjects
  - Biofeedback: 28 subjects
  - Sham biofeedback: 25 subjects
- 65 subjects completed the study
  - 12 (16%) dropped out (10 due to noncompliance, 2 due to health issues)

Biofeedback-Dyssynergia

Goals of Therapy

1. Teach diaphragmatic breathing exercise
2. Teach anal sphincter and pelvic floor relaxation
3. Improve rectal sensation
4. Eliminate sensory delay
5. Improve rectoanal coordination

Rao SS. et al. Gastroenterology. 2005
Global Bowel Satisfaction
≥ 20 mm VAS

No of CSBMs / Week

Rao et al. CGH 2007
**Balloon Expulsion Time**

- **Biofeedback**
  - Significance: $\n$ : $p = 0.0024$ vs Sham
  - $\&$ : $p = 0.0290$ vs Standard
  - $\$ : $p < 0.0001$ vs Baseline

- **Sham Feedback**
- **Standard**

Rao et al. CGH 2007
CONCLUSIONS

- Biofeedback Therapy
  - Effectively improves symptoms and anorectal function
  - This effect is mediated by modifying their physiologic behavior
  - Provides sustained improvement in bowel function

- Should be the preferred treatment for patients with dyssynergia, especially when patients fail Standard Therapy
Alarm symptoms: Weight loss, blood in stool, >50 years etc
Investigate and treat appropriately
Refer to specialist

Abdominal pain +++
Bloating +++
History / physical exam

IBS-C
Lifestyle / diet / pharmacologic management
Improved
No

Abdominal pain ±
Bloating +

Chronic Constipation
Lifestyle / diet / pharmacologic management
Improved
No

Improved

Refer to specialist
Chronic constipation is a common condition associated with a significant economic and health care burden.

Chronic constipation affects quality of life.

There are few high-quality studies evaluating efficacy of bulking agents, stool softeners, and stimulant laxatives in chronic constipation.

If no red flags are present, limit diagnostic testing and start empiric treatment.
  • Consider specialized testing if patient does not respond to initial treatment.
  • Consider biofeedback therapy for dyssynergia.

Lactulose, PEG 3350, lubiprostone, linaclotide, are FDA-approved therapies for constipation.

Therapies with novel mechanisms of action provide new alternatives for relieving the burden of chronic constipation.

Key Points
Thank you