Gastroparesis: Optimizing Management and Improving Outcomes

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Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L.

Gastroparesis

Definition: A chronic symptomatic disorder of the stomach characterized by delayed gastric emptying in absence of mechanical obstruction.

Symptoms:
nausea, vomiting,
early satiety, postprandial fullness, abdominal distension,
upper abdominal pain.

Diagnosis:
Symptoms
Upper endoscopy
Gastric emptying test
Causes of Gastroparesis

Three main causes
- Diabetic
- Postsurgical
  - Past: Vagotomy, resection for ulcers
  - Present: Nissen fundoplication, Bariatric surgery
- Idiopathic
  - Postviral in some

Other causes
- Metabolic Disorders: Hypothyroidism
- Generalized GI Motility Disorder: Intestinal pseudo-obstruction
- Medications: narcotics, anticholinergics

Clinical Characteristics of Patients with Gastroparesis
(146 Patients at Tertiary Motility Centers)

<table>
<thead>
<tr>
<th>Gender:</th>
<th>Female 82%</th>
<th>Male 18%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of Symptoms:</td>
<td>34 years</td>
<td></td>
</tr>
<tr>
<td>Symptoms:</td>
<td></td>
<td>Causes of Gastroparesis:</td>
</tr>
<tr>
<td>Nausea</td>
<td>92%</td>
<td>Diabetic 29%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>84%</td>
<td>Postsurgical 14%</td>
</tr>
<tr>
<td>Bloating</td>
<td>75%</td>
<td>Idiopathic 28%</td>
</tr>
<tr>
<td>Early Satiety</td>
<td>60%</td>
<td>Postviral 8%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>46%</td>
<td>Parkinson’s 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudoobstruction 4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scleroderma 4%</td>
</tr>
</tbody>
</table>

McCallum et al. 1998
**Trends of Gastroparesis-Related Hospitalizations**

**United States, 1995-2004**

Figure 1. Number of hospitalizations with gastroparesis as the primary diagnosis in the United States, 1995-2004.

- Hospitalizations: Gastroparesis as primary diagnosis increased +158%
- Gastroparesis as secondary diagnosis increased +136%.
- Diabetes-related increased +53%.
- All hospitalizations increased +13%.

Wang, Fisher, Parkman. AJG 2008

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**Gastric Emptying: Regional Gastric Function**

Gastric emptying reflects coordinated function of the fundus, corpus, antrum, pylorus, duodenum:
- Fundic relaxation and accommodation
- Antral contractions for trituration/grinding
- Pyloric sphincter opening for final emptying
Techniques to Evaluate Gastric Emptying

Scintigraphy:
Standard test
Variable methodology clinically
Standardization of Meal and Imaging

Wireless Motility Capsule:
Office Based Test, easily standardized
Gastric emptying / contractility
Empties with resumption of phase III
Measures Whole Gut Transit

GE Breath Test:
Office Based Tests, easily standardized
Presently used in Europe clinically
Used in US in research studies

Symptoms and Delayed Gastric Emptying

Symptoms of gastroparesis are not well correlated with gastric emptying.

Symptoms associated with delayed gastric emptying in patients with functional dyspepsia (idiopathic gastroparesis) are primarily postprandial fullness, nausea and vomiting.

In patients with diabetes, symptoms associated with delayed gastric emptying are abdominal bloating/fullness and upper abdominal pain.

In patients undergoing gastric emptying test, only nausea, vomiting, and early satiety were associated with delayed gastric emptying.

1499 patients undergoing GES (21.3% diabetics, 9.5% prior gastric surgery), 629 (42%) had increased retention at 4 hrs (>10%). The symptoms correlating with gastric retention at 4 hours included early satiety, vomiting, feeling excessively full after meals, and loss of appetite.
**General Principles for Treatment of Gastroparesis**

Correction of fluid, electrolyte, nutritional deficiencies

Identification and treatment of the underlying cause

Suppression or elimination of symptoms, primarily N/V

Quigley, Hasler, Parkman. Gastroenterology 2000; 120:263

**Therapeutic Approach to Gastroparesis**

Dietary manipulations

Strive for euglycemia in the diabetic patient

Prokinetic therapy

Antiemetic therapy

Analgesic therapy
**Dietary/Nutritional Treatment for Gastroparesis**

Diet modifications
- Low roughage,
  low fat, low fiber
- Small meals

More frequent meals (3 meals with 2 snacks)

Change from solid food to primarily liquid meals

Oral Nutrient Supplementation

Jejunostomy feeding tube for long-term

TPN, generally not recommended

**Current Status of Prokinetic Agents**

Metoclopramide (Reglan)  
FDA-approved agent for gastroparesis (12 w for DG  
Prokinetic and antiemetic
- CNS side effects in 10-20%

Domperidone (Motilium)  
Not to be released in USA.  
FDA IND/IRB  
Prokinetic and antiemetic  
Side effects: low-lactation, prolong QTc

Erythromycin  
GI side effects - N/V/Abd pain  
Tachyphylaxis to effect  
?Cardiac effects

Being studied:  
- 5HT-4 receptor agonists
- Motilin receptor agonists
- Ghrelin receptor agonists


**Metoclopramide for Diabetic Gastroparesis**

Randomized, double-blind, controlled trial of metoclopramide in 10 patients with diabetic gastroparesis

Metoclopramide increased gastric emptying

Overall symptoms and symptoms of vomiting were reduced during metoclopramide treatment.

Poor correlation between improved gastric emptying and decreased symptoms.

Metoclopramide improves symptoms of diabetic gastroparesis:
- Peripheral effect of gastric smooth muscle to increase gastric emptying
- Central effect on chemoreceptor vomiting zone to decrease nausea.


**A Double-blind Multicenter Comparison of Domperidone and Metoclopramide in the Treatment of Diabetic Patients with Symptoms of Gastroparesis**

93 type 1 diabetic patients with gastroparesis symptoms were treated with either domperidone 20 mg po QID or metoclopramide 10 mg po QID for 4 weeks.

Domperidone and metoclopramide were equally effective in alleviating symptoms of diabetic gastroparesis.

Adverse CNS effects were more severe and more common with metoclopramide than with domperidone:
- Somnolence, reduction in mental acuity.

Patterson, Abell, Rothstein, Koch, Barnett. Am J Gastro 1999;94:1230
**Domperidone in the Management of Symptoms of Diabetic Gastroparesis**

Single-Masked Study: 208/269 (77%) patients with diabetic gastroparesis improved on Domperidone 20 mg po QID

Randomized Placebo-Controlled, Double-Masked Withdrawal Phase: Placebo group had greater deterioration in total symptom scores compared to domperidone


**Erythromycin in the Short-Term and Long-Term Control of Dyspepsia Symptoms in Gastroparesis**

25 patients with gastroparesis

Treated with low dose erythromycin suspension (50-100 mg TID)

Randomized, Placebo-Controlled Trial of Botulinum Toxin A for the Treatment of Delayed Gastric Emptying

32 patients randomized to receive either Botox 200 units in 5 ml (n=16) or Saline 5 ml (n=16) into the pylorus.

Friedenberg, Palit, Parkman, Nelson. Am J Gastroenterology 2008

Antiemetic Agents for Gastroparesis

<table>
<thead>
<tr>
<th>Class of Agent</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prokinetic agents with antiemetic properties</td>
<td>Metoclopramide (Reglan)</td>
</tr>
<tr>
<td>(antagonize dopamine receptors)</td>
<td>Domperidone (Motilium)</td>
</tr>
<tr>
<td>Phenothiazine derivatives</td>
<td>Prochlorperazine (Compazine)</td>
</tr>
<tr>
<td>(antagonize dopamine receptors in area postrema)</td>
<td>Trimethobenzamide (Tigan)</td>
</tr>
<tr>
<td>Anticholinergic agents</td>
<td>Scopolamine patch</td>
</tr>
<tr>
<td>Antihistamines (H₁ receptor antagonists)</td>
<td>Diphenhydramine (Benadryl)</td>
</tr>
<tr>
<td></td>
<td>Promethazine (Phenergan)</td>
</tr>
<tr>
<td></td>
<td>Meclizine (Antivert)</td>
</tr>
<tr>
<td>Antiserotonergic (5-HT₃ receptor antagonists)</td>
<td>Ondansetron (Zofran)</td>
</tr>
<tr>
<td></td>
<td>Granisetron (Kytril)</td>
</tr>
<tr>
<td></td>
<td>Dolasetron (Anzemet)</td>
</tr>
<tr>
<td></td>
<td>Palonosetron (Aloxi)</td>
</tr>
<tr>
<td>Substance P/Neurokinin-1 Receptor Antagonists</td>
<td>Aprepitant (Emend)</td>
</tr>
</tbody>
</table>
Other Forms of Antiemetic Rx for Refractory Patients

Low dose Tricyclic Antidepressants

Marinol

Relief Band

Jejunostomy feeding tube

Venting gastrostomy tube

Gastric electrical stimulation

Tricyclic Antidepressants for Chronic Vomiting in Diabetic Patients

24 diabetic patients treated with tricyclic antidepressants for nausea and vomiting after an unsatisfactory response to prokinetic therapy.

TCAs: Amitriptyline, nortriptyline, desipramine.

Starting doses 10-25 mg/day; final maintenance dose: 10-75 mg/day.

Sawhney, Prakash Lustman, Clouse. DDS 2007;52:418.
Nortriptyline for Idiopathic Gastroparesis

Mean (95% CI) Change (score)

Weeks

Nortriptyline
Placebo

No. of Patients

Nausea Subscore

P=0.16

Fullness/Satiety Subscore

P=0.87

Bloating Subscore

P=0.27

Total GCSI

P=0.46

Mean (95% CI) Change (score)

Weeks

Nortriptyline
Placebo

No. of Patients

Maranki, Parkman et al.
DDS 2010

Gastric Electric Stimulation (Enterra) Therapy

High frequency, low energy, short pulse duration stimulation; not gastric pacing.

FDA Humanitarian Device Exemption (HDE) for treatment of chronic, intractable (drug refractory) nausea & vomiting secondary to diabetic or idiopathic gastroparesis.

Mechanism of action not elucidated:
Increase gastric emptying
Enhance fundic relaxation (accommodation)
Decrease gastric sensitivity
Affect afferent sensory pathways to central mechanisms for N/V

Effect of GES Based on GP Subtype and Main Symptom

Maranki, Parkman et al.
DDS 2010
Laparoscopic pyloroplasty for gastroparesis results in sustained symptom improvement

Retrospective review of prospectively collected data of 28 patients who underwent minimally invasive pyloroplasty alone as treatment for gastroparesis from Jan 2007 to Sept 2010.

A laparoscopic Heineke-Mikulicz pyloroplasty was performed in 26 of 28 patients.

GES T1/2 decreased from 320 to 112 min.

Improvements were seen at 1 month for nausea, vomiting, bloating, abdominal pain, and GERD symptoms.

Improvement persisted at 3 months for nausea, vomiting, bloating, abdominal pain and GERD symptoms.

Minimally invasive pyloroplasty provides excellent outcomes for patients with gastroparesis.


Management of Gastroparesis

Symptoms Suggestive of Gastroparesis
(Nausea, Vomiting, Early Satiety, Fullness)

Establish the Diagnosis of Gastroparesis
Upper endoscopy or Upper GI Series
Rule out other organic etiologies
E.g. ulcer disease, mechanical obstruction

Gastric Emptying Test
(GES with 4-hour EggBarley Meal)
Alternative Smart Pill or Breath Test

Delayed GE

No Improvement

Initial Treatments
Dietary modifications
Prokinetic (Metoclopramide)
Antiemetic (Compazine) IM or IMC
Glucose control

No Improvement

Other Treatment Trials
Other Prokinetic Agents:
Erythromycin
Domperidone
Other Antiemetic Agents:
Ondansetron

No Improvement

Consider Further Treatment Options
Symptom Modulator (TCA)
Botulinum toxin injection
Funding Infusion
Gastric Electrical Stimulation
Diabetic Gastroparesis

Associated with long-standing Insulin-Dependent Diabetes (T1DM).

Seen in T2DM (NIDDM), where rapid gastric emptying can occur early in the disease.

Frequently occurs with other diabetic complications neuropathy, retinopathy, nephropathy (“triopathy”)

Gastroparesis is analogous to neuropathy of vagus nerve

May cause difficulty with glycemic control: hypoglycemia

NB; Hyperglycemia also delays gastric emptying
**Treatment Approach to Gastroparesis**

Multiple Areas to Address

Hydration and Nutrition

Dietary Changes

Prokinetic Treatment

Antiemetic Treatment

Glucose Control in Diabetic Patients

Pain Control

Psychological

**Treatment of Gastroparesis**

**General Items**

Avoid medications that can delay stomach emptying

Glucose control for diabetic patients

**Diet**

low fiber and roughage

low in fat (fat increases CCK and delays GE)

Liquid nutrients are better tolerated over solid food

small meals, usually multiple 4-6/day

**Nutrition Consultation**

**Antiemetic Agents**

Compazine, Tigan (affect CNS vomiting center)

Ondansetron, a 5-HT-3 receptor antagonist

**Prokinetic Agents**

Metoclopramide, a dopamine receptor antagonist

Erythromycin, a motilin receptor agonist

Domperidone, a dopamine receptor agonist
### Prokinetic Medication Classes

<table>
<thead>
<tr>
<th>Class of Agent</th>
<th>Available</th>
<th>Special Circumstances</th>
<th>Under Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine antagonists</td>
<td>Metoclopramide</td>
<td>Domperidone</td>
<td>Itopride</td>
</tr>
<tr>
<td>Motilin agonists</td>
<td>Erythromycin</td>
<td>?Clarithromycin</td>
<td>Mitemcinal</td>
</tr>
<tr>
<td>Ghrelin agonists</td>
<td></td>
<td></td>
<td>ulimorelin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TZP-102</td>
</tr>
<tr>
<td>5-HT₄ agonists</td>
<td>Cisapride</td>
<td>Tegaserod</td>
<td>Renzapride</td>
</tr>
<tr>
<td>Mosapride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscarinic agonists</td>
<td>Bethanechol</td>
<td></td>
<td>AT-7505</td>
</tr>
<tr>
<td>Acetylcholinesterase inhibitors</td>
<td>Physostigmine</td>
<td>Neostigmine</td>
<td>YM443 (Z-338)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nizatidine LR</td>
</tr>
<tr>
<td>CCK receptor antagonists</td>
<td></td>
<td></td>
<td>Loxiglumide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dexloxiglumide</td>
</tr>
</tbody>
</table>

### Antiemetic Medication Classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine D2 antagonists</td>
<td>Metoclopramide, Domperidone</td>
</tr>
<tr>
<td></td>
<td>Prochlorperazine, Trimethobenzamide</td>
</tr>
<tr>
<td>Serotonin 5-HT3 antagonists</td>
<td>Ondansetron, Granisetron, Dolasetron, Tropisetron</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Desipramine, Nortriptyline, Amitriptyline</td>
</tr>
<tr>
<td>Muscarinic M1 antagonists</td>
<td>Scopolamine, Hyoscymine</td>
</tr>
<tr>
<td>Histamine H1 antagonists</td>
<td>Dimenhydrinate, Meclizine, Promethazine</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Marinol, Tetrahydrocannabinol</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Lorazepam</td>
</tr>
<tr>
<td>Neurokinin NK1 antagonists</td>
<td>Aprepitant</td>
</tr>
</tbody>
</table>
Initiation of Enteral Nutrition
Surgical Jejunostomy

Severe weight loss
(weight loss > 10% of usual body weight over 6 months)

Repeated hospitalizations for refractory gastroparesis intravenous hydration and/or intravenous medication.

Better absorption of medications to gain therapeutic levels when vomiting prevents this.

Gastric decompression: Gastrostomy/jejunostomy tube(s).

Gastric electrical stimulation improves symptoms from diabetic gastroparesis in a prospective study.

Enterra gastric electrical stimulation uses an implantable neurostimulator with a high-frequency, low-energy output.

A controlled, multicenter, prospective study to evaluate the safety and efficacy of Enterra therapy in patients with chronic intractable nausea and vomiting from diabetic gastroparesis (DGP).

Patients with refractory DGP (n = 55; mean age, 38 y; 66% female, 5.9 years of DGP) underwent treatment with Enterra gastric stimulation. After surgery, all patients had the stimulator turned on for 6 weeks and then they randomly were assigned to groups that had consecutive 3-month, cross-over periods with the device on or off. After this period, the device was turned on in all patients and they were followed up, unblinded, for 4.5 months.

In patients with intractable DGP, 6 weeks of initial GES therapy with Enterra reduced vomiting and gastroparetic symptoms. The double-blind cross-over portion over 3 months was not significant. Patients had improvements in subjective and objective parameters with chronic stimulation after 12 months of GES, compared with baseline.

Predictive Factors for Clinical Improvement with Enterra Gastric Electric Stimulation Treatment for Refractory Gastroparesis

The Temple Experience (2004-2006)

Overall, 14 of 28 (50%) patients felt improved. GCSI decreased by 12±7% from 3.3±0.2 to 2.7±0.2. Nausea/vomiting subscore improved by 30±7%.

Abdominal pain did not change.

Three Predictive Factors for Symptom Improvement:

Diabetic patients improved better than idiopathic patients

Patients with chief complaint of nausea/vomiting did better abdominal pain.

Patients taking regular narcotic analgesics at the time of implant had a poorer response compared to those not taking narcotics.

Gastric Electric Stimulation (Enterra) Therapy

Enterra Therapy is indicated for the treatment of patients with chronic, intractable (drug refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology.

FDA Statement on Enterra - Humanitarian Device Exemption (HDE) of a Humanitarian Use Device (HUD)

Still need medical insurance approval. Often initially denied – experimental.

Devised to improve gastric emptying.
Response does not depend on improving gastric emptying.
Other proposed mechanisms – fundic relaxation, afferent stimulation to central nausea/vomiting control mechanisms.
Bloating and Distension: Blowing up the Old Dogma

William D. Chey, MD
Professor of Medicine
University of Michigan

Functional Bowel Disorders

- Irritable bowel syndrome
- Functional Bloating
- Functional Constipation
- Functional Diarrhea
- Unspecified FBD

Rome III
Medical Definitions: Bloating vs. Abdominal Distension

- **Functional Bloating – Rome III definition**
  - Abdominal fullness, bloating or distension unrelated to obvious maldigestion (e.g., lactose intolerance) or excess consumption of poorly digestible but fermentable food stuffs (e.g., sorbitol, beans, wheat bran), in the absence of functional dyspepsia or IBS

  [Longstreth G., Gastroenterology 2006; 130:1480
  Whorwell NGM 2012;24:301]

- **Bloating = subjective sensation of fullness**

  [Longstreth G., Gastroenterology 2006
  Whorwell NGM 2012;24:301]
Medical Definitions: Bloating vs. Abdominal Distension

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- **Bloating = subjective sensation of fullness**

- **Distension = objective increase in abdominal girth**

Bloating is Common in IBS

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>87.4</td>
</tr>
<tr>
<td>Male</td>
<td>70.4</td>
</tr>
<tr>
<td>IBS-D</td>
<td>72.3</td>
</tr>
<tr>
<td>IBS-C</td>
<td>88.7</td>
</tr>
<tr>
<td>IBS-M</td>
<td>88.8</td>
</tr>
</tbody>
</table>

Ringel et al. CGH 2009;7:68
Bloating is Common in IBS

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramping</td>
<td>47 (13.9)</td>
</tr>
<tr>
<td><strong>Bloating</strong></td>
<td><strong>43 (12.8)</strong></td>
</tr>
<tr>
<td>Loose/watery stool</td>
<td>38 (11.3)</td>
</tr>
<tr>
<td>Straining</td>
<td>33 (9.8)</td>
</tr>
<tr>
<td>Urgency</td>
<td>31 (9.2)</td>
</tr>
<tr>
<td>Fear of cancer</td>
<td>28 (8.3)</td>
</tr>
</tbody>
</table>

Symptoms that Made Participants Decide to See a Doctor During the Past 12 Months

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain/discomfort</td>
<td>125 (37.1)</td>
</tr>
<tr>
<td>Cramping</td>
<td>108 (32.0)</td>
</tr>
<tr>
<td><strong>Bloating</strong></td>
<td><strong>95 (28.2)</strong></td>
</tr>
<tr>
<td>Urgency</td>
<td>85 (25.2)</td>
</tr>
<tr>
<td>Fear of cancer</td>
<td>81 (24.0)</td>
</tr>
</tbody>
</table>

Ringel et al. CGH 2009;7:68

Bloating does not discriminate between Normals and FGIDs

- Cross sectional population based study of VA employees
- Completed BDQ, SF-36
- 72% response rate (723/1069)

Tuteja et al. Am J Gastroenterol 2008;103:1241
Pathogenesis of Bloating & Distension

- Microbiome Fermentation
- Abdomino-phrenic dyssynergia
- Visceral Hypersensitivity
- Dyssynergic Defecation
- Abnl Gas Handling
- Air Swallowing

Villoria et al Am J Gastroenterol 2010;815
Whorwell Neurogastoenterol & Motil 2012;24:301

Comparison of LHBT Results Between IBS Patients and Healthy Controls

<table>
<thead>
<tr>
<th></th>
<th>IBS (n=277)</th>
<th>HC (n=64)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactase Malabsorption, n (%)</td>
<td>211 (76.2)</td>
<td>48 (75.0)</td>
<td>0.843</td>
</tr>
<tr>
<td>AUC, ppm.min</td>
<td>2,978 (1,058–5,693)</td>
<td>2,719 (1,071–5,366)</td>
<td>0.485</td>
</tr>
<tr>
<td>Lactose intolerance, n (%)</td>
<td>149 (53.8)</td>
<td>18 (28.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Intolerance symptoms

- Bloating, n (%) | 108 (39.0) | 9 (14.1) | <0.001 |
- Diarrhea, n (%)  | 79 (28.5)  | 6 (9.4)  | 0.001  |
- Pain, n (%)      | 87 (31.4)  | 7 (10.9) | 0.001  |
- Borborygmi, n (%) | 108 (39.0) | 14 (21.9) | 0.010  |
- Nausea, n (%)    | 16 (5.8)   | 2 (3.1)  | 0.586  |

AUC. area under the curve; HC, healthy control; IBS, irritable bowel syndrome; LHBT, lactose hydrogen breath test.
AUC is expressed as median (interquartile range), comparisons made by Mann-Whitney U test. Other variables are reported as number (Percentage), comparisons done using Pearson chi-square test.
Treatment Options for Bloating & Distension

- Diet
- Probiotics
- Prosecretories
- Antibiotics
- Prokinetics
- Biofeedback

Scmulson & Chang. Aliment Pharmacol Ther 2011;33:1071

Gluten Causes Symptoms in IBS Patients Without Celiac Disease

Mean Change in Symptoms Over 6 Weeks

- Overall symptoms
- Bloating
- Pain
- Tiredness

- Gluten (n=19)
- Placebo (n=15)

*P-value for analyses at Week 1 and entire study period.
Reprint permission has been requested.
**FODMAPs: Mechanism of Action**

- **Small intestine**
  - FODMAPs
  - ↑ water delivery
  - ↑ gas production

- **Large intestine**
  - Luminal distension
  - Altered motility
  - Pain, bloating, distension, wind, constipation +/- diarrhea

(Courtesy of Sue Shepherd, Ong, 2010, Barrett, 2009)

**Impact of FODMAP Diet on Breath Hydrogen Production and Symptoms**

- **Design**
  - Single-blind crossover study in 15 controls and 15 IBS patients
  - 2-day consumption of high-FODMAP diet (50 g/d) or low-FODMAP diet (9 g/d)

- **Results**
  - Higher levels of breath hydrogen with high FODMAP diet
  - GI symptoms and lethargy induced by high FODMAP diet in IBS patients but not controls

*Breath hydrogen production over time*

N=29

HFD=high-FODMAP diet; LFD=low-FODMAP diet

Daily Symptom Scores on low-FODMAP vs. Control Diet

![Chart showing symptom scores for Control and Intervention groups.](chart.png)


Treatment of Bloating & Distension

![Diagram showing treatment options for bloating and distension.](diagram.png)

Scmulson & Chang. Aliment Pharmacol Ther 2011;33:1071
Mean score changes at 4 weeks:
*B. infantis 35624 vs. Placebo for IBS

- Abdominal Pain
- Bloating
- Incomplete evacuation
- Gas
- Straining
- Bowel satisfaction
- Composite score

<table>
<thead>
<tr>
<th>Condition</th>
<th>Bifantis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Bloating</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Incomplete evacuation</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Gas</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Straining</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Bowel satisfaction</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Composite score</td>
<td></td>
<td>*</td>
</tr>
</tbody>
</table>

Whorwell, Am J Gastroenterol 2006; 101:1581

Probiotic VSL#3 Improves Flatulence and Retards Colon Transit in IBS

Average symptom scores over 4-8 wk treatment period

- Placebo
- VSL #3

n=24 each group *p=0.01

Kim HJ et al. NGM 2005; 17:687

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Pathogenesis of Bloating & Distension

Diet

Probiotics

Antibiotics

Prosecretories

Prokinetics

Biofeedback?

Scmulson & Chang. Aliment Pharmacol Ther 2011;33:1071

Rifaximin Reduces Gas-related Symptoms in Bloating Patients Without SIBO*

Overall Study Population

Patients With Global Relief, %

Baseline | End of Treatment | Post-treatment (10 days)
--- | --- | ---
Rifaximin (n=63) | Placebo (n=61)
41.3% | 22.9% | 28.6% | 11.5%

Patients With IBS (Rome II)

Patients With Global Relief, %

Baseline | End of Treatment | Post-treatment (10 days)
--- | --- | ---
Rifaximin (n=37) | Placebo (n=33)
40.5% | 18.2% | 27.0%
P=.04 | P=.05

Symptoms evaluated included abdominal pain, distension, number of bowel movements, stool consistency, and feeling of incomplete evacuation

*As determined by breath test.

## Efficacy of Rifaximin for Bloating in IBS

<table>
<thead>
<tr>
<th>Measure Outcomes</th>
<th>Response rates (%)</th>
<th>Weight</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rifaximin</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pimental</td>
<td>41.8</td>
<td>15.9</td>
<td>2.5%</td>
<td>25.9</td>
</tr>
<tr>
<td>Lembo</td>
<td>46.1</td>
<td>39.6</td>
<td>26%</td>
<td>6.5</td>
</tr>
<tr>
<td>Target 1</td>
<td>39.5</td>
<td>28.7</td>
<td>33.9%</td>
<td>10.8</td>
</tr>
<tr>
<td>Target 2</td>
<td>41.0</td>
<td>31.9</td>
<td>37.5%</td>
<td>9.1</td>
</tr>
<tr>
<td>Overall</td>
<td>41.6</td>
<td>31.7</td>
<td>100%</td>
<td>9.9</td>
</tr>
</tbody>
</table>

OR = 1.55; 95% CI = 1.23, 1.96; P < 0.001


## Pathogenesis of Bloating & Distension

- Diet
- Probiotics
- Prosecretories
- Antibiotics
- Prokinetics
- Biofeedback?

Scmulson & Chang. Aliment Pharmacol Ther 2011;33:1071
Chloride Channels in Intestinal Transport

Enterocytes

CFTR Channel
Linaclotide
Plecanatide

Ion Transport

Cl−

2Cl−

H2O

Na+

K+

K+

Na+

Na+

H2O

CIC− Channel
Lubiprostone

Tight junction

Lubiprostone Symptom Change: Responder vs Nonresponder

Baseline Score

Mean Change From Baseline

Abdominal Discomfort/Pain

Bloating*

Constipation Severity*

Stool Consistency†

Straining*

*0 (absent), 1 (mild), 2 (moderate), 3 (severe), 4 (very severe)
†0 (very loose [watery]), 1 (loose), 2 (normal), 3 (hard), 4 (very hard [little balls])

Drossman et al. APT 2009 29, 329–341
Effect of Linaclotide on Bloating in Chronic Constipation

![Graph showing the effect of Linaclotide on bloating in chronic constipation. The graph displays baseline and 12 week treatment data for Placebo, Linaclotide 145 µg, and Linaclotide 290 µg groups. The y-axis shows severity levels: Very severe, Severe, Moderate, Mild, and None. The x-axis shows trial weeks from 1 to 26. The graph indicates a statistically significant decrease in bloating severity with Linaclotide treatment compared to placebo, p≤0.0001 vs. placebo.]

Lembo et al. NEJM 2011; 365:527-36

Linaclotide Phase 3 IBS-C Trial

Weekly Change in Abdominal Symptoms

![Graphs showing weekly change in abdominal symptoms for Discomfort, Fullness, Bloating, and Cramping. The y-axis represents % change from baseline, and the x-axis represents trial weeks from 1 to 26. The graphs show a significant decrease in symptoms with Linaclotide treatment compared to placebo, p < 0.01 for each of the 26 Weeks in the Treatment Period.]


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Evidence-based Treatment of Bloating & Distension

Bloating & Distension

General Measures:
- Lifestyle
- Diet
- Probiotics

Diarrhea
- Antibiotics

Constipation
- ClC₂ activator
- GCβ agonists
- Prokinetics
- Biofeedback

Functional Bowel Disorders Clinic

888-229-7408
**Fecal Bifidobacteria Concentration in IBS Patients**

![Graph showing the correlation between baseline and change in Bifidobacteria concentration in IBS patients.](image)

Baseline [Bifidobacteria] log10/g vs. Change in [Bifidobacteria] log10/g

$r = -0.54 \ (P = 0.033)$

**Effect of Linaclotide on Change in Bloating Severity from Baseline to 12 Weeks in IBS-C**

![Bar chart showing the effect of Linaclotide on bloating severity.](image)

- **Baseline**
  - Placebo (n=797)
  - Linaclotide, 290 ug (n=805)

- **12 Weeks**
  - Placebo (n=797)
  - Linaclotide, 290 ug (n=805)

**Change in Bloating Severity**

- **Very severe**: -1.0
- **None**: -1.9*

* $p=0.0001$ vs. placebo

Phase 3 trials
Differentiating and Treating IBS-C and Chronic Constipation

Lin Chang, M.D.
Oppenheimer Family Center for Neurobiology of Stress
Division of Digestive Diseases
David Geffen School of Medicine at UCLA

Primary Causes of Chronic Constipation

Subtypes of Constipation

- Normal-transit constipation
- Slow-transit constipation
- Defecatory dysfunction
- IBS with constipation

Intestinal transit and stool frequency are within normal range (most common subtype)
Subtypes of Constipation

- Slow transit and IBS-C overlap in half of each group
- Systematic review found prevalence of STC to be 38%-80%

IBS-C: IBS with constipation; STC: slow-transit constipation


IBS & CIC: Common Functional Disorders

<table>
<thead>
<tr>
<th>Irritable Bowel Syndrome (IBS)</th>
<th>Chronic Idiopathic Constipation (CIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-15% of the US population</td>
<td>12-19% of the US population</td>
</tr>
<tr>
<td>Demographics</td>
<td>Demographics</td>
</tr>
<tr>
<td>- All ages (&lt;age 50)</td>
<td>- ≥ 40% over age 65</td>
</tr>
<tr>
<td>- Females &gt; males (2:1 to 4:1)</td>
<td>- Female &gt; male</td>
</tr>
<tr>
<td>12% of primary care and 28% of GI visits</td>
<td>7 million MD visits/ year</td>
</tr>
<tr>
<td>• 50% higher costs for direct costs vs. controls</td>
<td>• $3000/pt diagnostic work-up</td>
</tr>
<tr>
<td>• Indirect costs – absenteeism vs. impaired productivity</td>
<td>• $4500/pt for treatment</td>
</tr>
<tr>
<td></td>
<td>• Indirect costs – 60% impaired at work, 12% miss work/school average 2.5 days/month</td>
</tr>
</tbody>
</table>

ACG 2013 Annual Postgraduate Course • October 12-13, 2013
• Must include 2 or more of the following
  • In >25% of defecations
  • Hard or lumpy stool
  • Straining
  • Incomplete evacuation
  • Sensation of anorectal obstruction/blockage
  • Manual maneuvers necessary
  • <3 defecations/week
  • Loose stools rarely present without laxative use

Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with 2 or more of the following
  • Improvement with defecation
  • Onset associated with a change in frequency of stool
  • Onset associated with a change in form (appearance) of stool

Stool Form Correlates to Intestinal Transit Time

<table>
<thead>
<tr>
<th>THE BRISTOL STOOL FORM SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow Transit</td>
</tr>
<tr>
<td>Type 1</td>
</tr>
<tr>
<td>Type 2</td>
</tr>
<tr>
<td>Type 3</td>
</tr>
<tr>
<td>Type 4</td>
</tr>
<tr>
<td>Type 5</td>
</tr>
<tr>
<td>Type 6</td>
</tr>
<tr>
<td>Type 7</td>
</tr>
</tbody>
</table>

Rapid Transit
### Chronic Constipation vs. IBS-C

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Chronic Constipation</th>
<th>IBS-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Straining&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hard or Lumpy Stools&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Decreased BM Frequency&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>✓</td>
<td>+/-</td>
</tr>
<tr>
<td>Sensation of Incomplete Evacuation&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

- (+) Abdominal Pain
  - IBS-C
- (-) Abdominal Pain
  - Chronic Constipation

Presence or absence of abdominal pain and possibly BM frequency are the major differentiating features<sup>1,2</sup>.

---

### CC and IBS-C: Significant Overlap in Symptoms

- **89.5%** of IBS-C patients (n=201) meet criteria for CC (n=231) and **43.8%** of CC patients fulfill criteria for IBS-C without ROME III restriction that diagnosis may not overlap.

- While IBS-C patients report more pain/discomfort, ≈ **45%** of CC patients report some pain/discomfort.
- Patients with IBS-C had greater psychological distress than patients with CC.

Wong RK, et al. AJG 2010;105:2228-2234
Abdominal Pain is Main Predictor of having IBS-C

- At 12 months
  - <20% of CC patients met criteria for IBS (13% IBS-C, 5% IBS-M)
  - 25% of IBS-C patients met criteria for CC
  - In IBS-C and CC, only baseline predictor of having IBS-C rather than CC at 12 months was frequency of abdominal pain; not psychological distress or QoL


Differential Diagnosis of IBS With Constipation

Differential Diagnosis
Differential Diagnosis of Constipation

- Secondary constipation
  - Mechanical obstruction
  - Metabolic diseases
  - Painful anorectal conditions
  - Collagen-vascular disease
  - Neurologic diseases
  - Pregnancy
  - Medications
- Primary (idiopathic) constipation

Psyllium Improves Stool Frequency and Consistency in Occasional Constipation

- Placebo
- Psyllium 3.6 g TID for 2 weeks

1. Numeric change
2. Percent decrease

<table>
<thead>
<tr>
<th>Metric</th>
<th>Placebo</th>
<th>Psyllium 3.6 g TID for 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of formed stools per week</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Loose stools per week</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total stools per week</td>
<td>14</td>
<td>9</td>
</tr>
</tbody>
</table>

- Abdominal discomfort
- Straining

*N = 183


*P < 0.05
Long-Term Effectiveness of PEG 3350 in Chronic Constipation

Successful treatment after 6 months

% of patients

PEG

Placebo

* P<0.001


PEG + Electrolytes Improves Stool Frequency but not Pain in IBS-C

Spontaneous BMs

Abdominal discomfort/pain

PEG +E (1-3 13.8g PEG+E sachets/d), n=68
Placebo (sucrose), n=71

Chapman et al. AJG 2013
Chloride Channels in Intestinal Transport

Enterocytes

CFTR Channel
Linaclotide
Plecanitide

Ion Transport

Cl⁻ Cl² Channel

Lubiprostone

Tight junction

H₂O
Na⁺

K⁺

Na⁺ K⁺

2Cl⁻

H₂O
Na⁺

Effects of Lubiprostone on Number of Spontaneous Bowel Movements in CC

Mean SBMs per week

Baseline Week 1 Week 2 Week 3 Week 4

24 µg lubiprostone bid

Placebo

n = 242

Intent-to-treat population

SBM = spontaneous bowel movements


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Lubiprostone in IBS-C

- **Efficacy in clinical trials**
  - Significantly higher overall response vs. placebo\(^1\)
  - Grade 1B\(^2\)

- **Clinical practice tips**
  - Start at 8μg bid
  - Can increase to 24 μg bid if needed
  - Take with meals to reduce nausea

\(^2\)ACG IBS Task Force, Am J Gastro 2009; 104 (S1): S1-S35


---

Efficacy of Linaclotide in Chronic Constipation

**Responder** = ≥3 CSBM/wk & increase of ≥1 CSBM/wk for ≥ 9/12 wks

<table>
<thead>
<tr>
<th>Study</th>
<th>% Responders</th>
<th>L 145 mcg, n=430</th>
<th>L 290 mcg, n=418</th>
<th>Placebo, n=424</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>16(^<em>) 21(^</em>) 6(^*)</td>
<td>L 145 mcg, n=430</td>
<td>L 290 mcg, n=418</td>
<td>Placebo, n=424</td>
</tr>
<tr>
<td>303</td>
<td>21(^<em>) 19(^</em>) 3(^*)</td>
<td>L 145 mcg, n=430</td>
<td>L 290 mcg, n=418</td>
<td>Placebo, n=424</td>
</tr>
</tbody>
</table>

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

\(^*\)p≤0.0012

CSMB, complete spontaneous bowel movement
Efficacy of Linaclotide in IBS-C: 6/12 week responder primary end point

Composite Responder (6/12 Week APC + 1)

Responders (%)

Placebo N=403

Linaclotide 266 µg N=401

13.9%*

33.7%

*P<.0001, ITT population (266 µg vs placebo).


Linaclotide Phase 3 IBS-C trial: Abdominal pain over 26 weeks

Change in Abdominal Pain (%)

ITT population, observed cases, LS-means presented: P-values based on ANCOVA at each week. Bars represent 95% CI.

**Efficacy of Prucalopride (5-HT4 Agonist) in CC**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Prucalopride</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Miner 1999</td>
<td>121</td>
<td>183</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>Emmanuel 2002</td>
<td>10</td>
<td>39</td>
<td>27</td>
<td>38</td>
</tr>
<tr>
<td>Coremans 2003</td>
<td>17</td>
<td>27</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>Camilleri 2008</td>
<td>289</td>
<td>411</td>
<td>184</td>
<td>209</td>
</tr>
<tr>
<td>Quigley 2009</td>
<td>331</td>
<td>429</td>
<td>187</td>
<td>212</td>
</tr>
<tr>
<td>Tack 2009</td>
<td>374</td>
<td>476</td>
<td>217</td>
<td>240</td>
</tr>
<tr>
<td>Muller-Lissner 2010</td>
<td>146</td>
<td>231</td>
<td>55</td>
<td>72</td>
</tr>
</tbody>
</table>

**Total (95% CI)**
- 1796 events, 843 total, 100% weight
- 0.82 [0.76, 0.88]

---

**Summary**

- Chronic idiopathic (functional) constipation and IBS-C overlap
- Abdominal pain helps to differentiate IBS-C from chronic constipation and predict IBS-C status in future
- Evidence supports use of fiber, PEG, stimulant laxatives, lubiprostone, linaclotide, prucalopride in CC
- Evidence supports use of fiber, PEG, lubiprostone and linaclotide in IBS-C
- Fiber and laxatives have not been shown to improve abdominal pain in IBS-C