Abdominal pain in functional GI disorders

Hubert LOUIS
Service de Gastroentérologie, Hôpital Erasme

Hubert.louis@erasme.ulb.ac.be
Outline

- Functional GI disorders: from a clinician view
  - Common
  - Is it really functional?
  - Pain is often not the only symptom (dyspepsia, bloating)

- Treatment options
  - General measures
  - Diet
  - Medications
  - Non-pharmaceutical approaches
Social and economic impact of functional GI diseases

- Chronic gastrointestinal symptoms in the absence of any organic cause
  - Common: 25-50% of gastroenterologist’s consultations
  - Economic burden: second highest cause of absenteism after common cold, health-care utilization (repeated endoscopies, unnecessary surgery)
  - No decrease in life expectancy, affects the quality of life, family disruption

*Talley, Neurogastroenterol Motil 2010*
Chronic abdominal pain

- Differential diagnosis (many etiologies)
  - Active listening
  - Integration of historical data
  - Physical examination
  - Diagnostic strategy with confirmatory studies

- Characteristics of pain
  - Poorly localized
  - Negative diagnostic tests
  - Not readily-responding to gut-acting treatments
  - Central dysregulation with time
Perception of visceral stimuli

Normal

Peripheral

Central

Abnormal processing
Depression
Anxiety

“leaky filter”

Increased sensitivity of afferents
Increased intestinal distension

Boeckxstaens, Int J Colorectal Dis 2012
Outline

- Functional GI disorders: from a clinician view
  - Common
  - Is it really functional?
    - Pain is often not the only symptom (dyspepsia, bloating)

- Treatment options
  - General measures
  - Diet
  - medications
  - non-pharmaceutical approaches
Alarm symptoms and signs

- Anorexia
- Malnutrition
- Weight loss
- Nocturnal or progressive pain
- Bloody stools
- Anemia
- Familial history of CRC
Is it really functional? Reassurance for the patient or the physician?

Fecal calprotectin

Gunnarsson, Nat Clin Pr Gastroenterol 2008
Making a diagnosis of functional GI disorder is difficult

- Symptoms are non-specific
- No biological marker
- Clinician may be perplexed
- Make a positive diagnosis rather than a diagnosis of exclusion
  - Key issue: obtain a certain diagnosis while minimizing risks, at a reasonable cost
  - Routine follow-up visits with targeted diagnostic studies is a cost-effective approach
Functional gastrointestinal disorders (Rome III)

Functional esophageal disorders
  - Functional heartburn
  - Functional chest pain of presumed esophageal origin
  - Functional dysphagia
  - Globus

Functional gastroduodenal disorders
  - Functional dyspepsia
  - Belching disorders
  - Nausea and vomiting disorders
  - Rumination syndrome in adults

Functional bowel disorders
  - Irritable bowel syndrome
  - Functional bloating
  - Functional constipation
  - Functional diarrhea
  - Unspecified functional bowel disorder

Functional abdominal pain syndrome

Functional gallbladder and Sphincter of Oddi (SO) disorders
  - Functional gallbladder disorder
  - Functional biliary SO disorder
  - Functional pancreatic SO disorder

Functional anorectal disorders
  - Functional fecal incontinence
  - Functional anorectal pain
    - Chronic proctalgia
    - Proctalgia fugax
  - Functional defecation disorders

Functional disorders: neonates and toddlers
  - Infant regurgitation
  - Infant rumination syndrome
  - Cyclic vomiting syndrome
  - Infant colic
  - Functional diarrhea
  - Infant dyschezia
  - Functional constipation

Functional disorders: children and adolescents
  - Vomiting and aerophagia
  - Abdominal pain-related functional gastrointestinal disorders
  - Constipation and incontinence

Drossman, Gastroenterology 2006
Outline

- Functional GI disorders: from a clinician view
  - Common
  - Is it really functional?
  - Pain is often not the only symptom (dyspepsia, bloating)

- Treatment options
  - General measures
  - Diet
  - Medications
  - Non-pharmaceutical approaches
Pain is often not the only symptom

- Bloating
- Dyspepsia (nausea, early satiety…)
- Altered stool habits (constipation/diarrhea)
- Belching
- Flatulence
- Extra-intestinal symptoms
- Anxiety, depression
**Functional Dyspepsia: symptoms**

**Meal-related symptoms**
- Early satiation
- Bothersome postprandial fullness

**Meal-unrelated symptoms**
- Epigastric pain
- Epigastric burning

**Postprandial distress syndrome**

**Epigastric pain syndrome**

_Tack, Gastroenterology 2006_
Pathogenesis of functional dyspepsia

Gastric motor disorders
- Delayed gastric emptying
- Impaired accommodation

Other conditions
- Psychological distress
- Visceral hypersensitivity

Bacterial
- *H. pylori*
- Postinfectious (Salmonella, giardia)

Chemical
- Acid dysregulation or mucosal sensitivity
- NSAID
- Bile

Duodenal sensitivity to acid
Duodenal eosinophilia
Functional dyspepsia: algorithm

1. Patient with chronic or recurrent
   - postprandial fullness
   - early satiation
   - epigastric pain or
     - epigastric burning
   2. History and physical examination
   3. Alarm features?
   4. Coexisting frequent heartburn?
   5. Manage as gastroesophageal reflux disease
   6. Symptom improvement?
   7. Gastroesophageal reflux disease
   8. Consider test-and-treat for H. pylori?
   9. Symptom improvement?
   10. Dyspepsia with H. pylori
   11. Empirical therapy
   12. Symptom improvement?
   13. Dyspepsia not requiring further investigation
   14. Upper GI endoscopy with H. pylori testing
   15. Organic disorder that explains the symptoms?
   16. Any abnormality identified?
   17. Peptic ulcer malignancy esophagitis
   18. H. pylori positive?
   19. Symptom improvement?
   20. Eradication therapy
   21. Functional dyspepsia

Tack, Am J Gastroenterol 2010
Functional dyspepsia: algorithm

Dyspeptic symptoms

Endoscopy

Functional dyspepsia (eradicate if HP+)

Organic dyspepsia

Meal-related (PDS)

Meal-unrelated (EPS)

Prokinetic

Acid suppressive

Prokinetic

Acid suppressive

Acid suppressive

TCA if refractory

4-8 w PPI

Prokinetic

Acid suppressive

Prokinetic
Abdominal bloating

- Frequent symptom, women > men

Jiang, Gut 2008
Abdominal bloating

Subjective sensation (bloating) vs actual change in abdominal girth (distension)

Agrawal, Aliment Pharmacol Ther 2007
Whorwell, Neurogastroenterol & Motil 2012
Williams, J Neurogastroenterol & Motil 2012
Abnormal gas production

- Methane, hydrogen, nitrogen
- Production by bacterial fermentation of unabsorbed short-chain carbohydrates: lactose, sucrose, sorbitol
- Aerophagia (air swallowing), carbonated beverages
- Gut microbiota modifications (« dysbiosis »)

Agrawal, Aliment Pharmacol Ther 2007
Dietary sources of intestinal gas

- Noncaloric sweeteners
- Mannitol, sorbitol (chewing gum, candy)
- Beans and legumes: rafinose, stachyose
- Vegetables (broccoli, cauliflower, onions)
- Potatoes, sweet potatoes
- Soluble fiber supplements

Ong, J Gastroenterol & Hepatol 2010
Abdominal bloating: causes

- Impaired intestinal gas propulsion and clearance (retention in small bowel)

Salvioli, Gastroenterology 2005
Abdominal bloating: causes

- Impaired intestinal gas propulsion and clearance (retention in small bowel)
  - Increased by lipid meals, psyllium

- Visceral hypersensitivity (distorted perception, poor tolerance to gas retention)

*Serra, Gut 2001 & Gastroenterology 2002
*Agrawal, Aliment Pharmacol Ther 2007*
Abdominal bloating: causes

- Abdominal girth muscle dysfunction

![Diagram showing organic and functional causes of abdominal bloating.](image)

**Organic**

Normal abdominal accommodation reflex

**Functional**

Diaphragmatic descent

*Accarino, Gastroenterology 2009*
Outline

- Functional GI disorders: from a clinician view
  - Common
  - Is it really functional?
  - Pain is often not the only symptom (dyspepsia, bloating)

- Treatment options
  - General measures
    - Diet
    - Medications
    - Non-pharmaceutical approaches
Treatment of functional GI disorders

- Current therapies focus on symptom relief, not cure
- Patient-physician relationship and education
- Emerging nonpharmacological therapies
- Drug chosen depends on major symptom (IBSc ≠ IBSd)
- New drugs
Factors that can affect the patient-physician relationship

- **Patient**
  - Positive expectations from treatment
  - Readiness to enter into a therapeutic relationship
  - Readiness to take responsibility for self-care

- **Physician**
  - Listen actively
  - Empathise
  - Identify and respond to concerns
  - Validate
  - Reassure
  - Present treatment options
  - Set reasonable goals
  - Help patient take care on responsibility for care
  - Continuity of care

*Drossman, Aliment Pharmacol Ther 2007*
Putting patients first

- Functional GI disorders are multifactorial: think about both physiopathologic mechanisms and psychologic factors that are driving patient’s symptoms
- Explain the pathophysiologic mechanisms associated with symptoms
Placebo effect in functional GI diseases

Functional dyspepsia

Veldhuyzen van Zanten, Am J Gastroenterol 1996
Physician-patient relationship, placebo effect

- Reassurance, explanations, positive diagnosis, establish realistic expectations

Kaptchuk, BMJ 2008
Kaptchuk, Plos One 2010
Patient education

- Written resources, books, websites
  www.apssii.org

- Other healthcare professionals (nurses...)

Ringström, Eur J Gastroenterol Hepatol 2010
Functional GI disorders: from a clinician view
  - Common
  - Is it really functional?
  - Pain is often not the only symptom (dyspepsia, bloating)

Treatment options
  - General measures
  - Diet
    - Medications
    - Non-pharmaceutical approaches
60% of patients report worsening of symptoms after meals

30-50% of patients believe their symptoms represent a food allergy/intolerance
Food might cause symptoms

- Food allergy (uncommon: 1-3%)
- Stimulation of
  - Mechanoreceptors
  - Chemoreceptors
- Release of hormones / peptides
- Alterations in secretion
- Changes in osmolarity
- Fermentation of foods: impaired absorption → gas formation, luminal distension, bloating, laxative effect
- Common offenders: lactose, fructose and other fermentable carbohydrates, fiber, wheat
- Lactase deficiency leads to fermentation in the colon (↑ H₂, CO₂, methane)
- 30-35% adults are lactose-intolerant (more common in Africans and Asians)
- Treatment options: Lactose-free diet, lactase supplementation, soy milk
Fructose

- No enzyme present in human small intestine
- Efficiently absorbed in conjunction with glucose
- Fruits, honey, table sugar, corn syrup
- 11-70% intolerance estimated
Other fermentable foods

- Fructans (fructo-oligosaccharides)
  - Long chains of fructose molecules
- Galactans (galacto-oligosaccharides)
  - Short chains of sucrose and galactose
  - Raffinose
- Polyols
  - Sorbitol, mannitol, xylitol, maltitol
The low FODMAP diet

- **FODMAP = Fermentable Oligo- Di- and Monosaccharides And Polyols**

*Gibson and Shepherd, Clin Gastroenterol Hepatol 2008
Staudacher, J Hum Nutr Diet 2011*
Fiber

- Widely recommended to treat IBS symptoms
- Analysis of 7 high quality studies: no difference between fiber and placebo
- Produce bloating
Gluten

- Storage protein in wheat, barley, rye
- Genetically susceptible individuals (HLA-DQ2 and HLA-DQ8) develop an immune response to gliadin: celiac disease (prevalence 0.4 %)
- Gluten withdrawal: clinical response in a subgroup of patients (non celiac gluten sensitivity)

*Biesiekierski, Am J Gastroenterol 2011
Fasano, N Engl J Med 2012*
Diet: summary

- Low lactose and fructose diet
- Low-FODMAPs diet
- Discuss gluten free diet in a subset of patients with diarrhea
- Low lipid diet
- Avoid nutritional deficiencies
- Follow-up by dietetician?
Probiotics

- Numerous RCTs in IBS, different types of probiotics
- 6 systematic reviews suggest a modest benefit (bloating)

Whelan, Curr Opin Clin Nutr Metab Care 2011
Herbal medicine

- **STW 5 (Iberogast)**
  - Mixture of *Iberis amara* and 8 other herbal extracts
  - Meta-analysis of 6 RCTs: effective in functional dyspepsia

- **Peppermint oil**
  - Six RCTs showing efficacy against placebo in IBS

---

*Madish, Aliment Pharmacol Ther 2004*
*Krueger, Neurogastroenterol Motil 2009*
*Merat, Dig Dis Sci 2010*
## Non-pharmacological therapies

<table>
<thead>
<tr>
<th>Nonpharmacological treatments</th>
<th>Approximate number needed to treat</th>
<th>Adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibre, soluble&lt;sup&gt;48,126&lt;/sup&gt;</td>
<td>4–6</td>
<td>74% (any individual adverse event)</td>
<td>Two systematic reviews&lt;sup&gt;48,126&lt;/sup&gt; report heterogeneous outcomes; no serious or life-threatening adverse events reported</td>
</tr>
<tr>
<td>Fibre, insoluble&lt;sup&gt;48,126&lt;/sup&gt;</td>
<td>11</td>
<td>40% discontinued therapy because of adverse events</td>
<td>Weak evidence from RCTs and a systematic review to suggest efficacy over placebo&lt;sup&gt;47&lt;/sup&gt;</td>
</tr>
<tr>
<td>FODMAP diet&lt;sup&gt;56&lt;/sup&gt;</td>
<td>4–5</td>
<td>No adverse effects reported</td>
<td>No comments</td>
</tr>
<tr>
<td>Probiotics&lt;sup&gt;64&lt;/sup&gt;</td>
<td>4</td>
<td>Adverse event rate similar to placebo</td>
<td>Magnitude of benefit and the most effective species and doses remain uncertain</td>
</tr>
<tr>
<td>Peppermint oil&lt;sup&gt;48,126&lt;/sup&gt;</td>
<td>3</td>
<td>Not available</td>
<td>Adverse event rate comparable to placebo</td>
</tr>
</tbody>
</table>

_Halland, Nat Rev Gastroenterol Hepatol 2013_
Functional GI disorders: from a clinician view
  - Common
  - Is it really functional?
  - Pain is often not the only symptom (dyspepsia, bloating)

Treatment options
  - General measures
  - Diet
  - Medications
    - Non-pharmaceutical approaches
### Medications for functional GI diseases

**Table 2 | Selected pharmacological treatment for IBS**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Approximate number needed to treat</th>
<th>Approximate number needed to harm or adverse events</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatments for IBS-C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride channel activators (lubiprostone)\textsuperscript{72,129}</td>
<td>13</td>
<td>Up to 25% suffer nausea, no serious adverse events</td>
<td>Encouraging long-term data with less nausea reported\textsuperscript{72} than previously</td>
</tr>
<tr>
<td>5-HT\textsubscript{4} receptor agonists\textsuperscript{74}</td>
<td>10</td>
<td>20</td>
<td>Tegaserod was withdrawn because of concerns about cardiovascular safety\textsuperscript{75}</td>
</tr>
<tr>
<td>Guanylate cyclase C agonists (linaclootide)\textsuperscript{80,82–84}</td>
<td>4–5</td>
<td>20</td>
<td>Diarrhoea is the most common adverse event (5.3%)</td>
</tr>
<tr>
<td><strong>Treatments for IBS-D</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adsorbents\textsuperscript{85}</td>
<td>6</td>
<td>Not available</td>
<td>Adverse events equal to placebo</td>
</tr>
<tr>
<td>Rifaximin\textsuperscript{89}</td>
<td>11</td>
<td>8,971</td>
<td>No comments</td>
</tr>
<tr>
<td>5-HT\textsubscript{3} receptor antagonists (alosetron)\textsuperscript{89,90}</td>
<td>8</td>
<td>19</td>
<td>Rare reports of ischaemic colitis, use currently restricted to women under a risk management strategy\textsuperscript{84}</td>
</tr>
<tr>
<td>Tricyclic antidepressants/SSRIs\textsuperscript{89,126}</td>
<td>8</td>
<td>18</td>
<td>No comments</td>
</tr>
<tr>
<td>Antispasmodic agents\textsuperscript{48,126}</td>
<td>5</td>
<td>20</td>
<td>The most common adverse events are dry mouth, dizziness and blurred vision</td>
</tr>
<tr>
<td>Peppermint oil\textsuperscript{48,126}</td>
<td>3</td>
<td>Not available</td>
<td>Adverse event rate comparable to placebo</td>
</tr>
</tbody>
</table>

Abbreviations: 5-HT, 5-hydroxytryptamine; IBS-C, constipation-predominant IBS; IBS-D, diarrhoea-predominant IBS; SSRIs, selective serotonin reuptake inhibitor.

Halland, Nat Rev Gastroenterol Hepatol 2013
Prucalopride for chronic constipation

Tack, Neurogastr Motil 2013
Linaclotide

Bharucha, Gastroenterology 2010,
Table 2. Secondary and Additional End Points (Intention-to-Treat Population). 

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (N = 309)</th>
<th>Linaclotide, 145 μg Dose (N = 217)</th>
<th>P Value</th>
<th>Linaclotide, 370 μg Dose (N = 116)</th>
<th>P Value</th>
<th>Placebo (N = 219)</th>
<th>Linaclotide, 145 μg Dose (N = 113)</th>
<th>P Value</th>
<th>Linaclotide, 370 μg Dose (N = 202)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CSMFS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean no./wk</td>
<td>0.9</td>
<td>2.4</td>
<td>2.4</td>
<td>0.9</td>
<td>2.2</td>
<td>2.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline no./wk</td>
<td>0.5</td>
<td>1.9</td>
<td>&lt;0.001</td>
<td>2.0</td>
<td>&lt;0.001</td>
<td>2.0</td>
<td>&lt;0.001</td>
<td>2.7</td>
<td>&lt;0.001</td>
<td>2.9</td>
</tr>
<tr>
<td>CSMFS &lt;24 hr after first dose (% of patients)†</td>
<td>11.0</td>
<td>32.2</td>
<td>&lt;0.001</td>
<td>26.9</td>
<td>&lt;0.001</td>
<td>13.5</td>
<td>28.2</td>
<td>&lt;0.001</td>
<td>29.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increase of ≥2 CSMFS for 9 or 12 wk (% of patients)‡</td>
<td>11.0</td>
<td>39.2</td>
<td>&lt;0.001</td>
<td>37.0</td>
<td>&lt;0.001</td>
<td>13.0</td>
<td>31.0</td>
<td>&lt;0.001</td>
<td>40.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>SIBMs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean no./wk</td>
<td>3.2</td>
<td>5.2</td>
<td>5.1</td>
<td>3.0</td>
<td>5.3</td>
<td>5.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline no./wk</td>
<td>1.1</td>
<td>3.0</td>
<td>&lt;0.001</td>
<td>3.0</td>
<td>&lt;0.001</td>
<td>1.1</td>
<td>3.4</td>
<td>&lt;0.001</td>
<td>3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SIBM &lt;24 hr after first dose (% of patients)†</td>
<td>39.7</td>
<td>70.0</td>
<td>&lt;0.001</td>
<td>54.6</td>
<td>0.001</td>
<td>30.1</td>
<td>64.3</td>
<td>&lt;0.001</td>
<td>60.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increase of ≥2 SIBMs for 9 or 12 wk (% of patients)‡</td>
<td>12.9</td>
<td>41.0</td>
<td>&lt;0.001</td>
<td>37.0</td>
<td>&lt;0.001</td>
<td>16.3</td>
<td>39.0</td>
<td>&lt;0.001</td>
<td>46.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Stool consistency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BSFS score‡</td>
<td>3.0</td>
<td>4.3</td>
<td>4.3</td>
<td>2.9</td>
<td>4.2</td>
<td>4.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline score</td>
<td>0.8</td>
<td>1.9</td>
<td>&lt;0.001</td>
<td>1.8</td>
<td>&lt;0.001</td>
<td>0.6</td>
<td>1.8</td>
<td>&lt;0.001</td>
<td>2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Straining severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean straining score‡</td>
<td>2.7</td>
<td>2.1</td>
<td>2.1</td>
<td>2.7</td>
<td>2.1</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline score</td>
<td>−0.5</td>
<td>−1.1</td>
<td>&lt;0.001</td>
<td>−1.2</td>
<td>&lt;0.001</td>
<td>−0.6</td>
<td>−1.1</td>
<td>&lt;0.001</td>
<td>−1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Abdominal discomfort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean discomfort score‡</td>
<td>2.2</td>
<td>7.0</td>
<td>2.1</td>
<td>2.3</td>
<td>2.0</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline score</td>
<td>−0.3</td>
<td>−0.5</td>
<td>&lt;0.001</td>
<td>−0.4</td>
<td>0.006</td>
<td>−0.3</td>
<td>−0.5</td>
<td>&lt;0.001</td>
<td>−0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Decrease of ≥0.5 points in score for 9 or 12 wk (% of patients)‡</td>
<td>21.1</td>
<td>33.6</td>
<td>0.003</td>
<td>31.9</td>
<td>0.01</td>
<td>20.5</td>
<td>29.1</td>
<td>0.04</td>
<td>35.1</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean bleeding score‡</td>
<td>2.5</td>
<td>2.3</td>
<td>2.4</td>
<td>2.6</td>
<td>2.3</td>
<td>2.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline score</td>
<td>−0.5</td>
<td>−0.4</td>
<td>&lt;0.001</td>
<td>−0.4</td>
<td>0.005</td>
<td>−0.2</td>
<td>−0.4</td>
<td>&lt;0.001</td>
<td>−0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Decrease of ≥0.5 points in score for 9 or 12 wk (% of patients)‡</td>
<td>15.3</td>
<td>30.0</td>
<td>&lt;0.001</td>
<td>27.8</td>
<td>0.002</td>
<td>17.7</td>
<td>29.1</td>
<td>0.006</td>
<td>32.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Constipation severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean score§</td>
<td>3.0</td>
<td>7.3</td>
<td>2.5</td>
<td>3.0</td>
<td>2.4</td>
<td>2.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline score</td>
<td>−0.27</td>
<td>−0.90</td>
<td>&lt;0.001</td>
<td>−0.81</td>
<td>&lt;0.001</td>
<td>−0.31</td>
<td>−0.91</td>
<td>&lt;0.001</td>
<td>−0.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Decrease of ≥2 points in score for 9 or 12 wk (% of patients)‡</td>
<td>17.2</td>
<td>39.2</td>
<td>&lt;0.001</td>
<td>35.2</td>
<td>&lt;0.001</td>
<td>16.7</td>
<td>35.2</td>
<td>&lt;0.001</td>
<td>35.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Constipation relief</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean score§</td>
<td>3.6</td>
<td>2.6</td>
<td>2.8</td>
<td>3.4</td>
<td>2.8</td>
<td>2.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline score</td>
<td>−0.59</td>
<td>−1.30</td>
<td>&lt;0.001</td>
<td>−1.19</td>
<td>&lt;0.001</td>
<td>−0.57</td>
<td>−1.23</td>
<td>&lt;0.001</td>
<td>−1.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relief of constipation symptoms (% of patients)‡</td>
<td>16.7</td>
<td>54.8</td>
<td>&lt;0.001</td>
<td>46.8</td>
<td>&lt;0.001</td>
<td>20.5</td>
<td>39.9</td>
<td>&lt;0.001</td>
<td>47.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Treatment satisfaction, wk 12</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean score**</td>
<td>2.0</td>
<td>3.3</td>
<td>&lt;0.001</td>
<td>3.1</td>
<td>&lt;0.001</td>
<td>2.3</td>
<td>3.1</td>
<td>&lt;0.001</td>
<td>3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quite or very satisfied (% of patients)†</td>
<td>14.8</td>
<td>49.3</td>
<td>&lt;0.001</td>
<td>40.7</td>
<td>&lt;0.001</td>
<td>22.8</td>
<td>41.8</td>
<td>&lt;0.001</td>
<td>53.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Treatment continuation, wk 12</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean score†</td>
<td>3.5</td>
<td>3.8</td>
<td>&lt;0.001</td>
<td>3.6</td>
<td>&lt;0.001</td>
<td>3.2</td>
<td>3.6</td>
<td>0.01</td>
<td>3.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Quite or very likely to continue treatment (% of patients)†</td>
<td>46.4</td>
<td>64.5</td>
<td>&lt;0.001</td>
<td>57.4</td>
<td>0.03</td>
<td>50.2</td>
<td>57.7</td>
<td>0.14</td>
<td>61.9</td>
<td>0.023</td>
</tr>
</tbody>
</table>
# Medications for functional GI diseases

## Table 2 | Selected pharmacological treatment for IBS

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Approximate number needed to treat</th>
<th>Approximate number needed to harm or adverse events</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatments for IBS-C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride channel activators (lubiprostone)\textsuperscript{72,129}</td>
<td>13</td>
<td>Up to 25% suffer nausea, no serious adverse events</td>
<td>Encouraging long-term data with less nausea reported\textsuperscript{72} than previously</td>
</tr>
<tr>
<td>5-HT\textsubscript{4} receptor agonists\textsuperscript{74}</td>
<td>10</td>
<td>20</td>
<td>Tegaserod was withdrawn because of concerns about cardiovascular safety\textsuperscript{75}</td>
</tr>
<tr>
<td>Guanylate cyclase C agonists (linaclotide)\textsuperscript{80,82–84}</td>
<td>4–5</td>
<td>20</td>
<td>Diarrhoea is the most common adverse event (5.3%)</td>
</tr>
<tr>
<td><strong>Treatments for IBS-D</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adsorbents\textsuperscript{85}</td>
<td>6</td>
<td>Not available</td>
<td>Adverse events equal to placebo</td>
</tr>
<tr>
<td><strong>Rifaximin\textsuperscript{89}</strong></td>
<td>11</td>
<td>8,971</td>
<td>No comments</td>
</tr>
<tr>
<td>5-HT\textsubscript{3} receptor antagonists (alostreron)\textsuperscript{89,90}</td>
<td>8</td>
<td>19</td>
<td>Rare reports of ischaemic colitis, use currently restricted to women under a risk management strategy\textsuperscript{24}</td>
</tr>
<tr>
<td><strong>Tricyclic antidepressants/SSRIs\textsuperscript{89,123}</strong></td>
<td>8</td>
<td>18</td>
<td>No comments</td>
</tr>
<tr>
<td><strong>Antispasmodic agents\textsuperscript{48,126}</strong></td>
<td>5</td>
<td>20</td>
<td>The most common adverse events are dry mouth, dizziness and blurred vision</td>
</tr>
<tr>
<td>Peppermint oil\textsuperscript{48,126}</td>
<td>3</td>
<td>Not available</td>
<td>Adverse event rate comparable to placebo</td>
</tr>
</tbody>
</table>

Abbreviations: 5-HT, 5-hydroxytryptamine; IBS-C, constipation-predominant IBS; IBS-D, diarrhoea-predominant IBS; SSRIs, selective serotonin reuptake inhibitor.
# Pharmacotherapy in functional GI Disorders: new drugs in the pipeline

## Table 3 | Selected emerging and possible future pharmacological and nonpharmacological treatments for IBS

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Example of drug name</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs targeting visceral hypersensitivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin synthesis Inhibitors</td>
<td>LX-1031</td>
<td>Positive phase II trial data including favourable adverse event profile(^{101})</td>
</tr>
<tr>
<td>Neurokinin 1 receptor antagonists</td>
<td>AV608</td>
<td>Further research on this molecule suspended due to safety concerns;(^{104}) other neurokinin 1 receptor molecules might be useful</td>
</tr>
<tr>
<td>Cholecystokinin 1 antagonists</td>
<td>Dexloxiplumide</td>
<td>Limited human data emerging(^{106})</td>
</tr>
<tr>
<td>Peripheral opioid receptor antagonists</td>
<td>Asimadoline and JN-3848502</td>
<td>Promising findings from animal data not replicated in human studies thus far(^{139})</td>
</tr>
<tr>
<td><strong>Drugs targeting motility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT(_4) agonists</td>
<td>Velutrag, prucalopride, naronapride</td>
<td>Prucalopride effective in chronic constipation; data from trials in patients with IBS awaited</td>
</tr>
<tr>
<td>Corticotropin releasing factor antagonists</td>
<td>Pexacertin</td>
<td>Did not alter colonic transit in a large phase IIA study(^{122})</td>
</tr>
<tr>
<td><strong>Bile-acid modulators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile-acid blinder</td>
<td>Colesevelam</td>
<td>Case reports of efficacy and limited trial data(^{133})</td>
</tr>
<tr>
<td>Bile-acid-transporter inhibitor</td>
<td>A3309</td>
<td>Promising data from patients with chronic constipation(^{131})</td>
</tr>
<tr>
<td>Bile acid</td>
<td>Chenodeoxycholate</td>
<td>Healthy volunteer data demonstrating accelerated colonic transit(^{111})</td>
</tr>
<tr>
<td><strong>Drugs targeting Inflammation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-aminosalicylic acid</td>
<td>Mesalazine</td>
<td>No data from well-designed trials in patients with IBS</td>
</tr>
<tr>
<td>Mast cell stabilizers</td>
<td>Ketoif en, Sodium cromoglicate</td>
<td>Promising data from small uncontrolled trials(^{118})</td>
</tr>
<tr>
<td><strong>Centrally acting drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine receptor modulators</td>
<td>Dextofisopam</td>
<td>Improved stool consistency in a small trial, but concerns about higher rates of abdominal pain than with placebo(^{116})</td>
</tr>
<tr>
<td>Antiepileptic</td>
<td>Pregabalin and gabapentin</td>
<td>Physiological effect on rectal sensory threshold,(^{130}) but no clinical trials so far</td>
</tr>
<tr>
<td><strong>Nonpharmacological treatments targeting the microbiota or motility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faecal microbiota transplantation</td>
<td>Not applicable</td>
<td>Limited data from nonrandomized trials only(^{135})</td>
</tr>
</tbody>
</table>
Functional GI disorders: from a clinician view
- Common
- Is it really functional?
- Pain is often not the only symptom (dyspepsia, bloating)

Treatment options
- General measures
- Diet
- Medications
- Non-pharmaceutical approaches
Adressing stress and psychosocial factors

- Assess vulnerability factors (adverse life events)
- Triggers or stressors that precede onset and exacerbations by at least 3-6 months
- Acknowledge psychosocial factors if relevant (Stress, anxiety, catastrophizing, inflexibility)
- Consider referral for behavioural or psychotherapy or gut-directed hypnotherapy if indicated and patient motivated
Hypnotherapy in functional GI disorders

- Uses verbal guidance and a special mental state of enhanced receptivity to facilitate therapeutic psychological and physiological changes
- Proven efficacy in IBS, functional dyspepsia, non cardiac chest pain

Average 7-12 sessions
- ↓ medication use and consultation rate
- Long-term efficacy
- Availability?

Whorwell, Lancet 1984, Gastroenterology 2002
Other non-pharmacological therapies

- **Cognitive behavioural therapy**
  - Targets hyperarousal, visceral anxiety, catastrophizing and inflexible problem solving
  - Availability limited
  - Internet-delivered programmes (self-management)?

- **Mindfulness training**

- **Acupuncture**
  - not more effective than sham procedure

Ljotsson, Am J Gastroenterol 2010
Gaylors, Am J Gastroenterol 2011
Manheimer, Am J Gastroenterol 2012
## Non-pharmacological therapies

<table>
<thead>
<tr>
<th>Nonpharmacological treatments</th>
<th>Approximate number needed to treat</th>
<th>Adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypnotherapy\textsuperscript{127,128}</td>
<td>2–3</td>
<td>No reports of adverse events in published RCTs</td>
<td>Several RCTs in different settings and populations supporting long-term efficacy</td>
</tr>
<tr>
<td>Cognitive behavioural therapy\textsuperscript{39}</td>
<td>3</td>
<td>No reports of adverse events in published randomized trials</td>
<td>Can be effectively delivered using the internet\textsuperscript{40}</td>
</tr>
<tr>
<td>Exercise\textsuperscript{59}</td>
<td>6–7</td>
<td>No adverse effects reported</td>
<td>Single, RCT only, results only statistically significant for preventing a clinically important increase in symptoms</td>
</tr>
<tr>
<td>Biofeedback\textsuperscript{61}</td>
<td>Not available</td>
<td>No adverse events reported from single trial</td>
<td>Among responders to biofeedback, 10 of 16 IBS-C patients improved</td>
</tr>
</tbody>
</table>

*Halland, Nat Rev Gastroenterol Hepatol 2013*
Functional GI disorders are multifactorial: think about both physiopathologic mechanisms and psychologic factors that are driving patient’s symptoms

- Active listening, empathy, acknowledge psychosocial factors
- Treatment decisions based on (predominant) symptoms, interest and motivation of the patient
- Set realistic expectations and objectives
- Consider diet modifications (low FODMAPs)
- Consider behavioural treatments
- New drugs in the pipeline