Functional Dyspepsia
Management in the Rome IV era

Prof Tim Vanuytsel MD PhD

Department of Gastroenterology, University Hospitals Leuven
Translational Research Center for Gastrointestinal Disorders (TARGID)
Leuven Intestinal Failure and Transplantation (LIFT)
University of Leuven, Belgium
Organic gastrointestinal disorders

- Conventional diagnostic means identify underlying disease
Organic vs. Functional

**Organic gastrointestinal disorders**
- Conventional diagnostic means identify underlying disease

**Functional gastrointestinal disorders**
- In up to 50% of patients seen by gastroenterologists, conventional diagnostic means fail to explain the symptoms.
- In these patients symptoms are thought to be caused by disturbances of gastrointestinal motility and sensitivity
Functional Gastrointestinal Disorders
The ROME Process

Manning
Kruis
Rome I
Rome II
Rome III
Rome IV

Functional Gastrointestinal Disorders
The ROME Process

- **FUNCTIONAL GASTRODUODENAL DISORDERS**
  - Functional dyspepsia;
  - Chronic nausea and vomiting disorders
  - Belching disorders
  - Rumination syndrome

- **FUNCTIONAL ESOPHAGEAL DISORDERS**
  - Functional Chest Pain
  - Functional Heartburn
  - Reflux Hypersensitivity
  - Globus
  - Functional Dysphagia

- **FUNCTIONAL BOWEL DISORDERS**
  - Irritable bowel syndrome;
  - Functional bloating;
  - Functional constipation;
  - Functional diarrhoea

- **FUNCTIONAL ANORECTAL DISORDERS**
  - Faecal Incontinence Functional Anorectal Pain
  - Functional Defaecation Disorder
Functional Dyspepsia

**Dyspepsia**
symptoms thought to originate from the stomach / duodenum

- Uninvestigated dyspepsia
  - Routine Testing incl. endoscopy (70%)

- Functional dyspepsia
- Organic dyspepsia
  (ulcer, esophagitis, cancer, …)
Functional Dyspepsia

- Postprandial distress syndrome (PDS)
  - Meal-related symptoms (fullness, early satiation)

- Epigastric pain syndrome (EPS)
  - Meal-unrelated symptoms (epigastric pain and burning)

Mahadeva et al. Neurogastroenterol Motil 2016
Stanghellini et al. Gastroenterology 2016
Pathogenesis: Biopsychosocial Model

Dysregulated Brain-Gut Axis (bi-directional)

Psychosocial factors
- Life stress
- Psychologic state
- Coping
- Social support

Physiology
- Motility
- Sensation
- Inflammation
- Altered bacterial flora

Brain CNS → Gut ENS

Early life
- Genetics
- Environment

FGID
- Symptoms
- Behavior

Outcome
- Medications
- MD visits
- Daily function
- Quality of life

Drossman et al. Gut 1999
Tanaka et al. J Neurogastroenterol Motil 2011
Pathogenesis: Biopsychosocial Model

Impaired accommodation

45%

Delayed gastric emptying

30%

Hypersensitivity to gastric distention

35%
Functional Dyspepsia

- History taking can be difficult in patients with functional dyspepsia.
- Comorbidity with GERD, IBS and other functional GI disorders is common.
- Misinterpretation and erroneous reporting of symptoms is common.
- Sufficient clinic time is needed for FGID.
- Identify the most bothersome symptom or symptom complex.
- Pictograms are helpful.
Functional Dyspepsia
Cardinal Symptoms

- Fullness
- Early Satiation
- Epigastric Burning
- Epigastric Pain

PDS
EPS

Tack et al. Aliment Pharmacol Ther 2014
Functional Dyspepsia
Associated Symptoms

Upper Abdominal Bloating

Nausea

Belching

Vomiting

Tack et al. Aliment Pharmacol Ther 2014
Functional Dyspepsia
Endoscopy in Dyspepsia?

- Broad definition Dyspepsia
- Rome Criteria Dyspepsia

N=5389

Ford et al. Clin Gastroenterol Hepatol 2010
STARS I study: Primary care study in 17 countries
2741 patients (18-70) fulfilling definition of functional dyspepsia (Rome II)

Table 1. Significant Benign Endoscopic Abnormalities

| Total number of patients undergoing endoscopy | 2741 |
| Patients with significant abnormalities at endoscopy | 635/2741 (23%)^a |
| Endoscopic findings | |
| Esophagus: lesions | |
| Reflux esophagitis with erosions | 407 (14.8%) |
| Esophageal ulcers | 19 (0.7%) |
| Endoscopically suspected esophageal metaplasia | 13 (0.5%) |
| Stomach: lesions | |
| Gastric erosions | 169 (6.2%) |
| Gastric ulcers | 62 (2.3%) |
| Duodenum: lesions | |
| Duodenal erosions | 96 (3.5%) |
| Duodenal ulcers | 72 (2.7%) |

^aSome patients had more than one endoscopic abnormality.

Table 2. Upper Gastrointestinal Malignancies, Age, and Country of Origin

<table>
<thead>
<tr>
<th>Malignancies</th>
<th>Sex</th>
<th>Age</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus (n = 3)</td>
<td>Female</td>
<td>30</td>
<td>Canada</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>53</td>
<td>Denmark</td>
</tr>
<tr>
<td>Stomach (n = 3)</td>
<td>Female</td>
<td>51</td>
<td>Canada</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>50</td>
<td>Singapore</td>
</tr>
<tr>
<td>Duodenum (n = 0)</td>
<td>Male</td>
<td>58</td>
<td>Canada</td>
</tr>
</tbody>
</table>

Cost of detecting 1 cancer:
all: 118,000 euro (at 258 euro/endoscopy)
>50 years: 43,000 euro

Functional Dyspepsia Alarm Features?

- Unintentional Weight Loss
- Age > 55ys (35y in East Asia)
- Dysphagia (especially if progressive) or Odynophagia
- Persistent vomiting
- Evidence of GI bleeding: melena, hematemesis, …
- Iron-deficient Anemia
- Family History of Gastric or Esophageal Cancer
- Relevant abnormalities on physical examination

Stanghellini et al. Gastroenterology 2016
Functional Dyspepsia
Diagnostic Evaluation

- H. pylori test and treat
- PPI therapy
- Prokinetic therapy (in PPI failures and 1st line in PDS)

Symptoms suggestive of gastroduodenal involvement:
- Postprandial fullness, early satiation, epigastric pain, epigastric burning, nausea, vomiting,
  excessive belching, rumination

Flowchart:
1. History and physical exam
2. Alarm features?
   - Yes: UGI endoscopy w/wo biopsies
      - Abnormality identified?
         - Yes: Secondary dyspepsia
         - No: Further evaluation needed
   - No: Further evaluation needed
Functional Dyspepsia

- Postprandial distress syndrome (PDS)
  - Meal-related symptoms (fullness, early satiation)
- Epigastric pain syndrome (EPS)
  - Meal-unrelated symptoms (epigastric pain and burning)

Stanghellini et al. Gastroenterology 2016
Functional Dyspepsia

- Postprandial distress syndrome (PDS)
- Epigastric pain syndrome (EPS)

H. Pylori test and treat

PPI
H. pylori eradication

Most cost-effective treatment in FD

Limitations:
- Depends on the prevalence of HP
- High NNT: 12.5
- Therapeutic gain is late
  (significance at 6-12 months)
- Only tested in HP infected patients!

Moayyedi et al. Am J Gastroenterol 2017
Mahadeva et al. Neurogastroenterol Motil 2016
Other Antibiotics: Rifaximin

Global Dyspeptic Symptoms

95 Rome III FD (HP negative)
Hong-Kong, secondary and tertiary care
Rifaximin 400mg tid vs. placebo for 14 days

Tan et al. Aliment Pharmacol Ther 2017
Proton Pump Inhibitors

- NNT = 10
- No need for dose escalation!
- Aim for the lowest effective dose
- Discontinue treatment if no effect in 4-8 wk
- Differential effect in subgroups?

N=5,853
0.87 [0.82-0.94]

Moayyedi et al. Am J Gastroenterol 2017
Proton Pump Inhibitors

ELF trial: 54 patients with functional dyspepsia
4 wk treatment with lansoprazole 15mg vs. placebo

Suzuki et al. United European Gastroenterol J 2013
Proton Pump Inhibitors

54 patients with functional dyspepsia
4 wk treatment with lansoprazole 15mg vs. placebo

PPIs work for epigastric pain/burning (EPS), but not for fullness and satiety (PDS).

Suzuki et al. United European Gastroenterol J 2013
Functional Dyspepsia

Postprandial distress syndrome (PDS)

H. Pylori test and treat

Prokinetic drugs

Epigastric pain syndrome (EPS)

PPI

1-2 months, standard dose
Prokinetics

- Mainly old, low-quality studies
  Meta-analyses mainly rely on cisapride
- High risk of publication bias
- Most products are not available in Europe/US

Metoclopramide: Extrapyramidal S/
Domperidone: QTc prolongation
Clebopride: Extrapyramidal S/
Alizapride: Extrapyramidal S/
Itopride

Metoclopramide: Extrapyramidal S/
Domperidone: QTc prolongation
Clebopride: Extrapyramidal S/
Alizapride: Extrapyramidal S/
Itopride

N=8,788
NNT = 6

0.92 [0.88-0.97]

Moayyeddi et al. Am J Gastroenterol 2017

Cisapride: QTc prolongation -> withdrawn
Tegaserod: cardiac ischemia -> withdrawn
Prokinetics
Itopride

A Placebo-Controlled Trial of Itopride in Functional Dyspepsia

Gerald Holtmann, M.D., Nicholas J. Talley, M.D., Ph.D., Tobias Liebregts, M.D., Birgit Adam, M.D., and Christopher Parow, M.D.
Prokinetics
Itopride

Randomized study population

<table>
<thead>
<tr>
<th>Placebo (n=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itopride 50 mg tid (n=135)</td>
</tr>
<tr>
<td>Itopride 100 mg tid (n=135)</td>
</tr>
<tr>
<td>Itopride 200 mg tid (n=136)</td>
</tr>
</tbody>
</table>

Screened patients (n=606) | Completers (n=474)

8 weeks Screening | Treatment | 4 weeks Follow-up

Prokinetics
Itopride

**Symptom Score**
Leeds Dyspepsia Questionnaire

**Response Rate**
Symptom Free or Marked Improvement

*Holtmann et al. N Eng J Med 2006*
Gastric Accommodation

Nutrients in the G.I. tract (oropharynx, stomach, duodenum)

CNS

Vagal afferent

Vagal efferent

Excitatory Motor Neuron

ACh

NO

VIP

cGMP

Inhibitory Motor Neuron

Interneuron

ACh

5-HT?

5-HT1A receptor

Muscarinic auto-receptor

Nicotinic receptor

5-HT1-like receptor

5-HT4 receptor
Prokinetics
Buspirone (5HT1A agonist)

Healthy volunteers, single oral doses
Gastric Barostat

Van Oudenhove et al. Aliment Pharmacol Ther 2008
17 FD patients
Improved PDS symptoms with buspirone 10mg t.i.d.
(4 weeks, cross-over)
Prokinetics
Acotiamide

Dual Mechanism of Action:
• Blocker of muscarinic auto-receptors
• Blocks cholinesterase
• Accelerated gastric emptying
• Increased accommodation

Matsushita et al. Neurogastroenterol Motil 2016
Prokinetics
Acotiamide

Japanese phase III study

FD-PDS (Rome III)
Acotiamide 100mg t.i.d. vs. placebo

Matsueda et al. Gut 2012
Prokinetics
Acotiamide

Overall Treatment Evaluation

Elimination of Fullness, Bloating and Early Satiety

Responder: improved or extremely improved

NNT=6

NNT=16
Functional Dyspepsia

Postprandial distress syndrome (PDS)  Epigastric pain syndrome (EPS)

H. Pylori test and treat

Prokinetic drugs  PPI

PPI (or combo?)  Neuromodulators
Neuromodulators (Antidepressants)

Gut-brain modulators for functional GI disorders

**SSRIs**
(paroxetine, fluoxetine, sertraline, citalopram, escitalopram)
When anxiety, depression, and phobic features are prominent with FGIDs

**TCAs**
(amitriptyline, nortriptyline, imipramine, desipramine)
First-line treatment when pain is dominant in FGIDs

**Tetracyclic antidepressant**
(mirtazapine, mianserin, trazodone)
Treatment of early satiety, nausea/vomiting, weight loss and disturbed sleep

**SNRIs**
(duloxetine, venlafaxine, desvenlafaxin, milnacipran)
Treatment when pain is dominant in FGIDs or when side effects from TCAs preclude treatment
# Neuromodulators

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Psychotropic drugs</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>1.1.1 Antipsychotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hu 1986</td>
<td>17</td>
<td>50</td>
<td>33</td>
<td>50</td>
</tr>
<tr>
<td>Arienti 1994</td>
<td>4</td>
<td>15</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Song 1998</td>
<td>10</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>86</td>
<td>166</td>
<td>86</td>
<td>166</td>
</tr>
</tbody>
</table>

| 1.1.2 Tricyclic antidepressants |        |       |        |       |                     |      |
| Braak 2011           | 11     | 18    | 17    | 20    | 6.5%                | 2011 |
| Wu 2011              | 20     | 55    | 29    | 52    | 6.3%                | 2011 |
| Talley 2015a         | 46     | 97    | 58    | 97    | 9.4%                | 2015 |
| Subtotal (95% CI)    | 170    | 196   | 159   | 199   | 22.3%               |      |

| Total events         | 77     | 104   |                     |      |

| 1.1.4 Selective serotonin re-uptake inhibitors |        |       |        |       |                     |      |
| Tan 2012             | 77     | 98    | 74    | 95    | 11.3%               | 2012 |
| Talley 2015b         | 60     | 98    | 58    | 97    | 10.3%               | 2015 |
| Subtotal (95% CI)    | 137    | 132   | 125   | 132   | 22.2%               |      |

| Total events         | 137    | 132   |                     |      |

| 1.1.5 Serotonin-norepinephrine re-uptake inhibitors |        |       |        |       |                     |      |
| van Kerkhoven 2008   | 50     | 80    | 49    | 80    | 6.9%                | 2008 |
| Subtotal (95% CI)    | 50     | 80    | 49    | 80    | 6.9%                |      |

| Total events         | 50     | 80    |                     |      |

| Total (95% CI)       | 673    | 665   | 100.0%              | 0.78 [0.68, 0.91] |

| Total events         | 388    | 465   |                     |      |

Heterogeneity: Tau² = 0.04, Chi² = 36.33, df = 13 (P = 0.0005); I² = 64%
Test for overall effect: Z = 3.26 (P = 0.001)
Test for subgroup differences: Chi² = 28.44, df = 6 (P < 0.0001), I² = 78.9%

N = 1,241
NNT = 6

Ford et al. Gut 2017

Sulpiride
Levosulpiride
Amitriptyline
Sertraline
Escitalopram
Venlafaxine
Neuromodulators: Amitriptyline

Talley et al. Gastroenterology 2015
Neuromodulators: Amitriptyline

Adequate relief (%)

Placement: 40
Amitriptyline: 53
Escitalopram: 38

$P = 0.05^{\dagger}$

*T > 5 weeks of adequate relief

$^{\dagger}$Overall treatment effect from logistic regression model incorporating balancing factors
Neuromodulators: Amitriptyline

Amitriptyline is only useful to treat pain in patients with EPS, not in PDS.

Talley et al. Gastroenterology 2015
Neuromodulators: Mirtazapine

N=34 FD (Rome III) patients with >10% weight loss and no psychiatric comorbidity.
Neuromodulators: Mirtazapine

Dyspepsia symptom severity score

- Mirtazapine
- Placebo

Early satiety

- Mirtazapine
- Placebo

Body weight

- Mirtazapine
- Placebo

Meal volume tolerance

- Mirtazapine
- Placebo

Functional Dyspepsia

- Postprandial distress syndrome (PDS)
  - **H. Pylori test and treat**
    - Prokinetic drugs
      - PPI (or combo?)
        - Weight Loss: Mirtazapine
- Epigastric pain syndrome (EPS)
  - PPI
    - Psychotherapy
    - Nutritional Support
    - Experimental Treatment
  - Pain: Amitriptyline