Functional Dyspepsia

Michael Fried
Division of Gastroenterology and Hepatology
University Hospital Zurich, Switzerland
Dyspepsia

Functional Dyspepsia

Non-GI Causes
(cardiac disease, muscular pain, etc.)

Structural Dyspepsia
(GERD, PUD, pancreatic disease, gallstones, etc.)
Diagnostic Criteria* for Functional Dyspepsia

Must include one or more of the following:

- Bothersome postprandial fullness
- Early satiation
- Epigastric pain
- Epigastric burning

and

no evidence of structural disease (including upper endoscopy) to explain the symptoms

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Tack J et al, Gastroenterology, 2006;130:1466–1479
Pathophysiology?

Carbone F and Tack J. Dig Dis 2014, 32: 222-229
Post-infectious FD and IBS

Futagami S et al. Aliment Pharmacol Ther 2015; 41: 177-188
Do subtypes make sense?

- 27% non-specific
- 31% overlapping

Lack of discriminant value of dyspepsia subgroups

Talley et al. Gastroenterology 1993
Bytzer et al. Scand J Gastroenterology 1992
Dyspepsia: a symptom complex

< 0.1% 1 symptom; 99% >2 symptoms; > 80% >5

Tack J et al, Gastroenterology, 2006;130:1466–1479
Meta-analysis, 151 papers included, N= 5389 patients

Main differential diagnoses for dyspepsia

1. Peptic ulcer (chronic)
2. GERD (w/wo esophagitis)
3. Malignant disease
4. Functional dyspepsia

Diagnosis after exclusion

Organic causes of dyspeptic symptoms

- Peptic ulcer disease
- GERD
- Medications (ASA/NSAIDS, Abx)
- Gastroparesis
- Gastric neoplasm
- Cholelithiasis, choledocholithiasis
- Pancreatitis (acute or chronic)
- Carbohydrate malabsorption
- Ischemic bowel disease
- Other GI malignancy (ep. Pancreatic cancer)
- Systemic disease (DM, Thyroid, Parathyroid, CTD)
- Intestinal parasites
Medications and dyspepsia

• NSAR cause dyspepsia in up to 20% of the patients (including COX-2 inhibitors)
• COX-2 inhibitor consumption decreases, but low dose aspirin use increases
• Identify:
  - Alendronat
  - Acarbose
  - Metformin
  - Orlistat
  - Digitalis
  - Theophylline
  - Potassium
  - Antibiotics (Erythromycin)

Hawkey et al. Gut 2003
Bytzer et Hallas. Aliment Pharmacol Ther 2000
Ofman et al. Arthritis Rheum 2003
Etiology of dyspeptic symptoms?

- Malignancy <1%
- Barrett's esophagus 2%
- Reflux esophagitis 20%
- Endoscopy-negative reflux disease 20%
- Peptic ulcer disease 10%
- Functional dyspepsia

Overland MK. Med Clin N Am; 2014; 98: 549-564
## Alarm symptoms and signs

<table>
<thead>
<tr>
<th>History</th>
<th>Signs</th>
<th>Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Weight loss</td>
<td>• Fever</td>
<td>• Anemia, Fe-deficiency</td>
</tr>
<tr>
<td>• Dysphagia</td>
<td>• Pathological status</td>
<td>• Leukocytosis</td>
</tr>
<tr>
<td>• Recurrent vomiting</td>
<td>• GI bleeding signs</td>
<td></td>
</tr>
<tr>
<td>• Icterus</td>
<td></td>
<td>• CRP ↑</td>
</tr>
<tr>
<td>• FA: Ca / Celiac d.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Onset &gt; 45 yrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Age > 45 or any alarm symptom as predictor of major endoscopic findings

To scope or not? Benefit of upper gi endoscopy

- **Canadian trial** (7004 pts <45 years, dyspepsia, no alarm symptoms)
  - 7% «significant» diagnoses
    - 31% normal
    - 30% gastritis
    - 23% reflux esophagitis

- **Asian trial** (387 pts, 45 years, dyspepsia, no alarm symptoms)
  - higher patients satisfaction by endoscopy (40 % vs 22 %)

- **Danish trial** (FD pts, 317 completed)
  - reassurance by endoscopy
  - cost-effective (but PPI at that time expensive)

_Mahadeva: Gut 2008. 57: 1214-20_  
Abdominal sonography?

- explains only rarely patients symptoms
- therapeutic gain only 1-3%
  - exclusion of pancreas pathology
  - gallbladder stones mostly incidental
- not recommended in patients < 45 years

DGVS-Leitlinien – Z Gastroenterol 2001; 39:937-956
General therapeutic measures in FD?

- Explanation of benign nature of disease ("re-assurance")

- Good patient-doctor relationship

- Dietary counseling (diet assessment, more meals, smaller portions, less fat, avoidance of nutrients which induce symptoms)

- Healthy lifestyle

Talley et al. Am J Gastroenterol 2005
Lacy et al. AP&T 2012
Functional dyspepsia – always PPI?

Metaanalysis (2007), 3725 patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talley, ref 61</td>
<td>Low dose</td>
</tr>
<tr>
<td>Blum, ref 83</td>
<td></td>
</tr>
<tr>
<td>Hengels, ref 84</td>
<td></td>
</tr>
<tr>
<td>Peura, ref 85</td>
<td></td>
</tr>
<tr>
<td>Wong, ref 86</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standard</td>
</tr>
<tr>
<td>Talley, ref 61</td>
<td>Low dose</td>
</tr>
<tr>
<td>Blum, ref 83</td>
<td></td>
</tr>
<tr>
<td>Bollinger, ref 85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standard</td>
</tr>
</tbody>
</table>

- PPI effective in patients with EPS and refluxlike symptoms, less effective in patients with PDS-type dyspepsia
- Lower dose equivalent to standard dose (e.g.: 10 mg vs. 20 mg omeprazole)

41 % (PPI) vs. 32 % (placebo)
\[ \text{RR- reduction} = 10 \% \ (95\% \text{ CI, } 2.7\%–17.3\%) \rightarrow \text{NNT 14} \]

PPI

• Basic therapy
• Effect independent of dose
• More effective in EPS with refluxlike symptoms

• Newer data
  – Japan: PPI monotherapy better than H2-RA + prokinetic for PDS
  – China: PPI more effective for treatment of epigastric burning than pain, postprandial fullness, early satiety

Symptom improvement after HP -Eradication?

- metaanalysis (Cochrane database) 2006, 21 RCT / 3566 pts.
- H. pylori eradication has a small (but significant) effect in H. pylori positive functional dyspepsia
- NNT = 15

Suzuki et al, J Neurogastroenterol Motil 2011; 17
Antidepressants for functional dyspepsia?

12 heterogenous small studies: relative risk reduction 45% vs placebo

2/4 studies with levosulpiride

Antidepressants

- **Amitryptiline** (Saroten®; 3x10mg/d)
- Japanese RCT, 27 FD patients with no response to H2-RA/prokinetics

*Otaka M et al. APT 2006; 21S:42-46*
Hypnotherapy?

126 patients randomized to
- hypnotherapy  (3 not completed)
- supportive therapy  (13 not completed)
- conventional treatment  (10 not completed)

Calvert EL et al. Gastroenterol 2002;123:1778-85
Functional dyspepsia – prokinetics?

Metaanalysis 2007, 27 studies:

- relative risk reduction (symptom free): 33% with prokinetic vs. placebo
- NNT=6

BUT:
- no longterm data
- 21/27 studies with cisapride (unavailable)
- domperidone (Motilium®) and metoclopramide (Paspertin®): less effective than cisapride

*Hiyama T et al. J Gastroenterol Hepatol 2007;22: 304-10*

*Veldhuyzen, van Zanten, Am J Gastroenterol 2001; 96: 689-696*
**Prokinetics: Levosulpiride** (Dogmatil®)

- **Action**
  - peripheral and central D2-receptor antagonist, partial ENS 5-HT4 agonist

- **Effects**
  - more potent than domperidone, metoclopramide and cisparide to reduce FD symptoms
  - similar efficacy to accelerate gastric emptying as cisapride

- **Dose**
  - 3x25mg - 3x50mg/d (Sanofi-Aventis, 50mg capsules)

- **Side effects**
  - gastrointestinal, tachykardia, prolactin elevation

Acid-suppressive drug, e.g., PPIs, H2 receptor blockers

Fundic relaxant drugs:
- M1 and M2 muscarinic receptors antagonists, e.g., acotiamide
- 5HT₁₆ receptor agonists, e.g., buspirone, tandospirone

Other mechanisms:
- Targeting visceral hypersensitivity, e.g., κ-opioid receptor agonist fedotozine
- Anti-inflammatory, e.g., montelukast, cromolyn
- Antidepressants, e.g., amitriptyline

Prokinetic drugs:
- 5-HT₄ receptor agonists, e.g., cisapride, prucalopride, cintapride
- Dopamine-2 receptor antagonists, e.g., domperidone, metoclopramide
- Mixed dopamine-2 receptor antagonists/cholinesterase inhibitor, e.g., itopride
- Motilin receptor agonists, e.g., macrolides, camical
- Ghrelin receptor agonists, e.g., TZP-101, TZP-102, RM-131
Take home messages

- FD: disturbed motility, sensitivity, inflammation, brain factors
- GI infections are risk factors for FD
- Low predictive value of FD symptoms for a positive diagnosis
- Alarm symptoms do not reliably predict organic disease
- Patients with FD should at least have once a gastroscopy; value of ultrasound is uncertain
- PPIs are basic FD therapy, independent if patients present reflux-like symptoms or not
- HP eradication is effective in a small subgroup
- Some (amitryptiline) antidepressants are effective to treat FD
- Hypnotherapy has a long-term effect on FD symptoms
- Prokinetics (sulpiride; acotiamide) should be tried if PPI, HP eradication and antidepressants have failed
Pierre-Auguste Renoir. Le déjeuner des canotiers