Functional Dyspepsia

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Major Causes of Endoscopy-negative Dyspepsia

- Structural and functional disease
  - Peptic ulcer disease
  - Gastroesophageal reflux (often diagnosed even if no esophagitis, heartburn rare and/or PPI fails)
  - Malignancy (gastric, esophageal, liver)
  - Drugs (all NSAIDs)
  - Pancreatic disease (chronic pancreatitis); *not* gallstones
  - Gastroparesis (vomiting, weight loss, very rare!)

- **Functional dyspepsia (60%)**
  - No structural or biochemical explanation found

Talley, *Gastroenterology* 1998; 114: 582
Talley, *Gastroenterology* 2003; 125: 1219
Celiac Disease and Dyspepsia?

- Positive celiac serology higher in dyspepsia (7.9%) vs. controls (3.9%), but not significant (OR 1.89; 95% CI 0.90-3.99)
- Prevalence of biopsy-proven celiac following positive serology higher (3.2% in cases vs. 1.3% in controls), but not significant (OR 2.85; 95% CI 0.60-13.38)

Am Fam Physician. 2007 15;76:1795-1802
Rome III
Functional Dyspepsia

Epigastric pain syndrome (EPS):
- Epigastric pain
- Epigastric burning

Postprandial distress syndrome (PDS):
- Postprandial heaviness or fullness
- Early Satiation

meal-related FD
Epidemiology of FD (Rome III)

Of 1000 Swedish subjects:
- 202 (20%) uninvestigated dyspepsia
- 157 (16%) FD
- 52 Epigastric Pain Syndrome (EPS): 33% of FD
- 122 postprandial distress syndrome (PDS): 78%
- 17 EPS and PDS overlap: 11%

Of 1033 Italian subjects:
- 156 (15%) uninvestigated dyspepsia
- 114 (11%) FD
- 55 Epigastric Pain Syndrome (EPS): 48% of FD
- 77 postprandial distress syndrome (PDS): 68%
- 18 EPS and PDS overlap: 16%

Epigastric Pain Syndrome (EPS)

- No association with anxiety or depression

Postprandial distress syndrome (PDS)

- Major anxiety
  (5.1 vs. 3.2; OR=4.35, 95% CI: 1.81-10.46)

- Use of NSAIDs
  (OR=2.75, 95% CI: 1.38-5.50)

- Low education level
  (OR=1.73, 95% CI: 1.04-2.87)
Pre-morbid Anxiety Increases Risk of Functional Dyspepsia

- Prospective Australian population data
- Controls (n=626) followed for 12 years (1997-2009)

![Graph showing odds ratio for different conditions with anxiety and non-anxiety groups.](image)

Koloski, Jones & Talley DDW 2010
Risk Factors for FD

- Olmsted County, MN
- Nested case-control study, dyspepsia (n = 52) and healthy controls (n = 40)
- Independent risk factors for dyspepsia adjusted for age, sex, BMI and PPI:
  1. Positive family history
     (OR = 4.7, 95% CI = 1.5-14.9)
  2. Sleep difficulty
     (OR = 8.2, 95% CI = 2.2-31.5)
  3. High somatic score
     (OR = 5.6, 95% CI = 1.5-20.7)
Traditionally, FD is a diagnosis of exclusion - peptic ulcer, GERD, malignancy (rare!)

In FD, meal related symptoms are characteristic

Diagnostic meal testing to positively identify FD?
Symptoms of Functional Dyspepsia are Induced by a Standard Meal

Test meal 60 g white bread, egg, 300 ml water consumed within 10 min (250 kcal: 14 g protein, 26 g carbohydrate, 10 g fat)
Non-invasive Assessment of Fundic Dysaccommodation and Visceral Sensation (*drink & puke test*)

- Nutrient drink test
- Water load test
- Meal challenge

Promote selection of patients with true post-prandial symptoms (=FD) for targeted therapy?

Functional Dyspepsia
Traditional Pathophysiology

1/3 Impaired accommodation

1/3 Delayed gastric emptying

1/3 Hypersensitivity to gastric distention

- Functional dyspepsia with early satiety and weight loss
- Functional dyspepsia but symptom associations controversial (nausea, vomiting and postprandial fullness)
- Functional dyspepsia with pain, belching and weight loss?
Gastric Emptying is Abnormal in Population Based (Non-health Care Seeking) Dyspeptic Subjects

*P values vs asymptomatic controls

Gastric Volume Changes in Health and Disease

Normal

Meal

Fundic accommodation or receptive relaxation

**Functional Dyspepsia**

Abnormal Fundic Relaxation in Response to Meal

**Dyspepsia:** 40%

- Normal fundic accommodation or receptive relaxation
- Impaired fundic accommodation with a redistribution of food to antrum

Tack et al. *Gastroenterology* 1998; 115:1346-52
Accommodation Reflex

Possible pathways for which experimental data exists

- Vagal afferent
- Gl tract
- Sumatriptan 5HT4 agonists Iberogast
- Inhibitory motor neuron
- NO

Nicotinic receptor
5-HT receptor

Visceral Hypersensitivity (barostat)

Tack et al, *Gastroenterology* 2001; 121: 526
Boeckxstaens et al, *Am J Gastroenterol* 2002; 97: 40

Prevalence (% of patients)

<table>
<thead>
<tr>
<th></th>
<th>Normal sensitivity</th>
<th>Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Yellow</td>
<td></td>
</tr>
<tr>
<td>Organic dyspepsia</td>
<td>Yellow</td>
<td>Orange</td>
</tr>
<tr>
<td>Functional dyspepsia</td>
<td>Yellow</td>
<td>Orange</td>
</tr>
</tbody>
</table>

Strain gauge

Pressure selector

Ct P
• FD patients failed to activate pACC, to deactivate dorsal pons during distension, and to deactivate amygdala during sham by PET

• Arousal-anxiety-driven failure of pain modulation?

• Gastric sensitivity and abuse history independently influence gastric sensation as well as brain activity in FD

Van Oudenhove et al. *Gastroenterology*. 2010 in press
Infection and Functional Dyspepsia: *H. pylori* Gastritis

H. pylori a Cause of FD?

Eradication therapy beats placebo but is this a non-specific antibiotic effect (no trials in Hp negative cases)?

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum 98</td>
<td>0.92 (0.81,1.03)</td>
<td>13.4</td>
</tr>
<tr>
<td>McColl 98</td>
<td>0.85 (0.77,0.93)</td>
<td>23.0</td>
</tr>
<tr>
<td>Koelz 03</td>
<td>0.95 (0.81,1.11)</td>
<td>8.0</td>
</tr>
<tr>
<td>Talley(Orchid) 99</td>
<td>0.97 (0.85,1.11)</td>
<td>12.0</td>
</tr>
<tr>
<td>Talley(USA) 99</td>
<td>1.07 (0.86,1.34)</td>
<td>4.2</td>
</tr>
<tr>
<td>Miwa 00</td>
<td>0.91 (0.70,1.18)</td>
<td>2.9</td>
</tr>
<tr>
<td>Malfertheiner 03</td>
<td>0.95 (0.85,1.06)</td>
<td>17.6</td>
</tr>
<tr>
<td>Varannes 01</td>
<td>0.83 (0.68,1.00)</td>
<td>5.6</td>
</tr>
<tr>
<td>Froehlich 01</td>
<td>0.86 (0.60,1.24)</td>
<td>1.5</td>
</tr>
<tr>
<td>Koskenpato 01</td>
<td>0.91 (0.78,1.07)</td>
<td>8.1</td>
</tr>
<tr>
<td>Gisbert 04</td>
<td>0.76 (0.40,1.46)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hsu 01</td>
<td>0.93 (0.66,1.33)</td>
<td>1.6</td>
</tr>
<tr>
<td>Van Zanten 03</td>
<td>0.94 (0.65,1.35)</td>
<td>1.5</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.91 (0.87,0.96)</td>
<td>13.4</td>
</tr>
</tbody>
</table>

NNT = 17 (95% CI 11 - 33)

New onset of Dyspepsia Post Salmonella Gastroenteritis

AGE = acute gastroenteritis

Bacterial Dysentery and FD

- Cohort study Walkerton, Ontario, Canada 2002-2003 – follow-up 2008
- Of 2597 subjects eligible, 1088 (42%) provided data for analysis: 706 (65%) acute gastroenteritis
- Risk for dyspepsia at 8 years in exposed by Rome II 2.30 (95% CI 1.63-3.26)
  - Prevalence of dyspepsia higher in females; smokers; premorbid IBS; anxiety or depression; >7 days diarrhea or cramps during acute illness
• Rotavirus infection leads to transient delayed gastric emptying
• Giardia intestinalis produces mainly post infectious FD
• Salmonella spp. and Campylobacter jejuni cause terminal ileitis and colitis, associated equally with both postinfectious FD and postinfective IBS
Presumed Post-infectious FD

![Bar chart showing prevalence of various conditions](chart.png)

- H. Pylori infection: 19%
- Delayed emptying: 25%
- Hypersensitivity to distention: 35%
- Impaired accommodation: 69%

* P < 0.05

Tack et al. *Gastroenterology* 2002; 122: 1738
Cytokine release and CD4+$\alpha$4$\beta$7+CCR9+ lymphocytes correlated with symptom intensity pain, cramps, nausea, vomiting.

Delayed gastric emptying correlated ($r=0.78$, $p=0.02$) with CD4+$\alpha$4$\beta$7+CCR9+ lymphocytes, and IL-1$\beta$, TNF-α and IL-10 secretion.
Clusters of eosinophils in D1 observed in 26 FD (51%) vs. 10 controls (21%) (p=0.003)
Duodenal Eosinophilia (UK)

- 155 patients (mean age 55 years, 59% females) with normal duodenal biopsies randomly selected
- Controls: mean duodenal eosinophil count 15/5HPFs; prevalence of duodenal eosinophilia 22.5%
- Postprandial distress syndrome (PDS) mean eosinophil counts (20.2/5HPF, p<0.04) and prevalence of duodenal eosinophilia (47%, p<0.04) higher
- Duodenal eosinophilia associated with allergy (OR 5.04, 95% CI 2.12-11.95, p<0.001) but not IBS or medications

Walker, Talley et al. *Aliment Pharmacol Ther.* 2010
Eosinophilia in FD

- What is the pathogenesis?
- Hypersensitivity?
  - Acid, allergen, pathogen
- Utility of treating duodenal eosinophilia in FD?

Smooth muscle cell

Lipid mediators
Leukotrienes (LT)
PAF

Cytokines
IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, IL-18, TGF-α1β, TNF

Cytotoxic secretory products
EPO, MBP, ECP, EDN

Nerve

Mast cell

Lymphocyte

Eosinophil cluster

NGF
VIP
Substance P

MBP

LT, PAF, IL-13

IL-4

Antigen presentation
## G-Protein (GNβ3) Polymorphisms

<table>
<thead>
<tr>
<th></th>
<th>FD %</th>
<th>Controls %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>7.1</td>
<td>3.6</td>
</tr>
<tr>
<td>CT</td>
<td>32.1</td>
<td>55.5</td>
</tr>
<tr>
<td>CC</td>
<td>60.7</td>
<td>41.1</td>
</tr>
</tbody>
</table>

CC: OR = 2.2  
95% CI 1.1-4.3

**Amplified signal transduction responses**

**Diminished signal transduction responses**

Holtmann, Talley et al. *Gastroenterology* 2004
Candidate Genotypes Associated with Functional Dyspepsia

- FD (n = 112)
- Healthy controls (n = 336)
- FD higher prevalence of T allele GNB3 C825T vs. controls (OR = 1.60, 95% CI: 1.03-2.49, P = 0.038)

Functional Dyspepsia: Rome III Subgroup Pathogenesis?

Functional dyspepsia

- Postprandial distress syndrome (PDS): Meal-related FD
  - Impaired accommodation
  - Delayed emptying
  - Duodenal hypersensitivity/inflammation.

- Epigastric pain syndrome (EPS): Meal-unrelated FD
  - H. pylori infection
  - Immune activation
  - Visceral sensitivity
  - Brain pain pathways
Response to Acid Suppression

<table>
<thead>
<tr>
<th>Patient sub-group</th>
<th>Risk ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux group</td>
<td>0.76 (0.66-0.88)</td>
</tr>
<tr>
<td>Epigastric pain group</td>
<td>0.85 (0.79-0.92)</td>
</tr>
<tr>
<td>Dysmotility group</td>
<td>1.02 (0.92-1.13)</td>
</tr>
</tbody>
</table>

Favors PPI therapy  Favors placebo
PPI Withdrawal Induces Dyspepsia

Niklasson et al. Am J Gastroenterol. 2010

58 Screened participants

- 4 Screen failures

54 Eligible participants

- 4 Excluded *H. pylori* positive

50 Randomly allocated

- 25 Allocated to pantoprazole
- 25 Allocated to placebo

2 Drop out

23 In analysis

25 In analysis

**Mean symptom score**

- **Start of therapy**
- **Cessation of therapy**

* indicates statistical significance.
<table>
<thead>
<tr>
<th>Study</th>
<th>Bismuth</th>
<th>Risk ratio (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang et al</td>
<td></td>
<td>0.82 (0.52-1.30)</td>
<td>22.6</td>
</tr>
<tr>
<td>Kazi et al</td>
<td></td>
<td>0.41 (0.21-0.82)</td>
<td>19.2</td>
</tr>
<tr>
<td>Lambert et al</td>
<td></td>
<td>0.79 (0.43-1.44)</td>
<td>20.5</td>
</tr>
<tr>
<td>Loffeld et al</td>
<td></td>
<td>1.19 (0.52-2.69)</td>
<td>17.4</td>
</tr>
<tr>
<td>Valra et al</td>
<td></td>
<td>0.21 (0.11-0.39)</td>
<td>20.2</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td></td>
<td>0.58 (0.32-1.04)</td>
<td></td>
</tr>
</tbody>
</table>

**Favors bismuth salts**

**Favors placebo**

**Sucralfate:**

RRR = 29%;
95% CI -40%, 62%)
NOT statistically significant
Fundus Relaxing Drugs: A Therapeutic Target in FD

- Serotonin 5HT$_4$ agonists: cisapride
- Serotonin 1 agonists: sumatriptan (5HT$_{1p}$), buspirone (5HT$_{1a}$)
- Selective serotonin reuptake inhibitors (some!)
- STW 5
Functional Dyspepsia: RCT of Herbal Drug STW 5

- *Angelicae radix* (Garden angelica)
- *Cardui mariae fructus* (Milk thistle fruits)
- *Carvi fructus* (Caraway fruits)
- *Chelidonii herba*
- *Iberis amara* (Bitter candy tuft)
- *Liquiritiae radix* (Liquorice root)
- *Matricariae flos* (Chamomile flowers)
- *Melissae folium* (Balm leaves)
- *Menthae piperitae folium* (Peppermint leaves)

GIS Sum Score (M±SD) [Score points]

- Day -7
- Day 0
- Day 14
- Day 28
- Day 56

* = $P < 0.05$

STW 5 in Healthy Men Relaxes the Gastric Fundus

- STW5 increased proximal gastric volume (max volume; control 104 ± 12 mL, STW5 174 ± 23 mL, P < 0.05)

Intrabag volume, as mean of 10-minute segments, after oral administration of 1.1 mL control solution or Iberogast, with 50 mL water

Amitryptiline and visceral hypersensitivity

Intra-balloon volume (ml)

- Fullness
- Discomfort
- Pain

Abdominal pain rating

- Placebo
- Amitryptiline

n = 7

*
Venlafaxine Not Efficacious

- Randomized, double-blind, placebo-controlled n=160
- Persistent dyspeptic symptoms, negative EGD
- 8 weeks venlafaxine XR (2 wks 75 mg once daily, 4 wks 150 mg once daily, and 2 wks 75 mg once daily)
- 56% and 73% of participants completed treatment with venlafaxine or placebo

 Clin Gastroenterol Hepatol. 2008;6:746-52
Functional Dyspepsia Treatment Trial (FDTT): NIH UO1 (Talley)

Amitryptiline vs. Escitalopram vs. Placebo 12 weeks (6 mo. follow-up)

- Mayo Clinic (Florida, Arizona, Rochester)
- 6 sites around the USA; McMaster (Moayyedi)
- We would welcome referrals

http://clinicaltrials.gov/ct2/show/NCT00248651
<table>
<thead>
<tr>
<th>Therapeutic intervention</th>
<th>Efficacy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H. pylori eradication</strong></td>
<td>36% vs 30% placebo; NNT 18</td>
<td>Meta-analysis of 13 RCTs</td>
</tr>
<tr>
<td>PPIs</td>
<td>33% vs 23% placebo; NNT 9</td>
<td>Meta-analysis of 8 RCTs</td>
</tr>
<tr>
<td><strong>H₂-receptor antagonists</strong></td>
<td>More effective than placebo for epigastric pain + postprandial fullness only</td>
<td>Meta-analysis of 11 RCTs</td>
</tr>
<tr>
<td>Antidepressants – TCAs</td>
<td>???</td>
<td>Single RCT demonstrating efficacy by PP analysis only</td>
</tr>
<tr>
<td>Antacids</td>
<td>No better than placebo</td>
<td>1 RCT only</td>
</tr>
<tr>
<td>Bismuth salts</td>
<td>No better than placebo</td>
<td>Meta-analysis of 5 RCTs</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>No better than placebo</td>
<td>Meta-analysis of 2 RCTs</td>
</tr>
</tbody>
</table>

Saad & Chey, *Aliment Pharmacol Ther* 2006; 24: 475
Functional Dyspepsia

- FD often misdiagnosed as gastroesophageal reflux disease or gastroparesis
- Rome III criteria for FD (EPS, PDS): increasingly accepted
- FD remains a diagnosis of exclusion
- Almost all meal related – a diagnostic test?
- H. pylori an uncommon cause
- Acid suppression 1\textsuperscript{st} line (usually fails)
- Gastroduodenal dysfunction common
- Duodenal eosinophilia: a novel target?
- Role of antidepressants?