Clinical Approach to the Patient with Dyspepsia

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Case:

42 year old female reports a long history of epigastric burning which is particularly bothersome after a meal. She denies heartburn, regurgitation, vomiting or dysphagia. She states that her symptoms have been worse over the past 6 months. She admits to feeling stressed about a recent job change and has not been sleeping well. She has lost 8 lbs over the past 6 months. She has been using OTC ranitidine without benefit.

Because of the worsening symptoms and weight loss, she undergoes an EGD which reveals no peptic ulcer disease or esophagitis. A rapid urease test is negative for *H. pylori*. 
Dyspepsia vs. Functional Dyspepsia: A Gastroenterologist’s perspective

“A patient entering the endoscopy unit has dyspepsia. A patient leaving the endoscopy unit has functional dyspepsia.”

Colin Howden, 2000
Prevalence of Endoscopic Findings in Individuals with Dyspepsia

Systematic Review and Meta-analysis including 9 studies

<table>
<thead>
<tr>
<th>Endoscopic finding</th>
<th>Number of studies</th>
<th>Number of subjects</th>
<th>Pooled prevalence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosive esophagitis</td>
<td>7</td>
<td>2067</td>
<td>13.4%</td>
<td>1.3-35.1</td>
</tr>
<tr>
<td>Barrett’s esophagus</td>
<td>6</td>
<td>1982</td>
<td>1.0%</td>
<td>0.03-3.4</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>9</td>
<td>2597</td>
<td>8.0%</td>
<td>6.0-11.0</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>6</td>
<td>2284</td>
<td>3.2%</td>
<td>2.0-4.7</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>6</td>
<td>2284</td>
<td>3.4%</td>
<td>1.6-5.9</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>6</td>
<td>1982</td>
<td>0.25%</td>
<td>0.05-0.6</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>6</td>
<td>1982</td>
<td>0.1%</td>
<td>0.02-0.3</td>
</tr>
</tbody>
</table>

Rome III: Diagnostic Criteria* for Functional Dyspepsia

Must include

1. **One or more of:**
   
   a. Bothersome postprandial fullness
   
   b. Early satiation
   
   c. Epigastric pain
   
   d. Epigastric burning

   **AND**

2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

*Tack, et al. Gastroenterol 2006;130:1466
Functional Dyspepsia: Rome III Subgroups

PDS
- Postprandial Distress Syndrome
  - Postprandial fullness
  - Early satiation

EPS
- Epigastric pain Syndrome
  - Intermittent epigastric pain/burning

Tack, et al. Gastroenterol 2006;130:1466
Pathogenesis of Functional Dyspepsia

Visceral Hypersensitivity

Microbiome Inflammation Post-infectious

Altered Brain-Gut Interactions

Abnormal upper GI motor & reflex functions

Genetic Factors

Psychosocial Factors

Functional Dyspepsia

Saad & Chey. Aliment Pharmacol Ther 2006;24:475
Current Management of Functional Dyspepsia

- H. pylori eradication
- Prokinetic therapy
- Antisecretory therapy
Dietary Recommendations for Functional Dyspepsia: What’s the Evidence?

- Efficacy of dietary interventions has not been carefully studied in Functional Dyspepsia

- Smaller meals may better tolerated
  - Patients develop fullness and other symptoms with smaller volumes of a nutrient drink or water vs. controls
  - FD symptoms directly related to overall calorie intake

- Avoid high fat meals
  - Ingestion of fat or intraduodenal lipid infusion leads to more symptoms in patients vs. controls
  - Fat but not carbohydrate intake directly related to symptoms

Feinle-Bisset, Neurogastroenterol Motil 2006; 18:608
Pilichiewicz, Clin Gastroenterol Hepatol 2009;317
Cochrane Meta-Analysis of *H. pylori* Cure for Functional Dyspepsia

- 17 RCTs (3566 patients)
- *Hp* eradication therapy vs. placebo or short course of PPI

<table>
<thead>
<tr>
<th>%</th>
<th>Symptom Improvement (range)</th>
<th>Therapeutic Gain (%)</th>
<th>NNT (95% CI)</th>
<th>RRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hp cure</td>
<td>36 (15-75)</td>
<td>7</td>
<td>14</td>
<td>10 (10-25)</td>
</tr>
<tr>
<td>Placebo</td>
<td>29 (7-51)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12/17 trials did not show significant benefits with *Hp* eradication

*Moayyedi et al. Cochrane Collaboration Feb. 2006*
**H. pylori** Cure for Functional Dyspepsia: HEROES Trial

The Rationale for Antisecretory Therapy in Functional Dyspepsia

- Gastric acid secretion in FD similar to controls\textsuperscript{1}
- Acid hypersensitivity
  - Lowered threshold of mechanosensitive afferents\textsuperscript{2,3}
    - Reduced antral motility, jejunal hypercontractions\textsuperscript{3}
  - Increased symptoms with duodenal acid infusion\textsuperscript{3,4}
- Increased duodenal acid exposure\textsuperscript{4-6}
  - Decreased fasting clearance of exogenous acid
  - Decreased fasting duodenal motor activity
  - More symptoms with duodenal acid infusion
- Overlap of GERD and dyspeptic symptoms\textsuperscript{7}

\textsuperscript{1} Bechi et al. \textit{Dig Dis Sci} 1992; 37:378
\textsuperscript{2} Coffin et al. \textit{Am J Physiol} 2001; 280:G904
\textsuperscript{3} DiStefano et al. \textit{Neurogastro Motil} 2009; 21:712
\textsuperscript{4} Sansom et al. \textit{Gastroenterol} 1999; 116:515
\textsuperscript{5} Lee et al. \textit{Am J Gastro} 2004; 99:1765
\textsuperscript{6} Ishii et al. \textit{J Sm Muscle Res} 2010; 46:1
\textsuperscript{7} Tack et al. \textit{Gut} 2005; 54:1370
Cochrane Meta-Analysis of PPI therapy for Functional Dyspepsia

- 10 RCTs (3347 patients)
- PPI for 2-8 weeks was superior to placebo in relieving FD symptoms

<table>
<thead>
<tr>
<th>% No or minimal symptoms</th>
<th>Therapeutic Gain (%)</th>
<th>NNT (95% CI)</th>
<th>RRR (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>34</td>
<td>9</td>
<td>10 (7-33)</td>
</tr>
<tr>
<td>Placebo</td>
<td>25</td>
<td></td>
<td>No assymetry by funnel plot</td>
</tr>
</tbody>
</table>

Moayyedi et al. Cochrane Collaboration 2007
Esomeprazole for Functional Dyspepsia

Overall Response Rates (%)

Week 4
Eso QD/BID: 26.8
Placebo: 26.3

Week 8
Eso QD/BID: 39.2
Placebo: 32.7

* P = 0.02
N = 1150
Eso 40 mg QD or BID
Europe, South America, Canada, Singapore

Talley et al. Aliment Pharmacol Ther 2007;26:673
### PPI for Functional Dyspepsia: Is a 1 week trial adequate?

Properties at 8 weeks according to treatment response in week 1

<table>
<thead>
<tr>
<th>Week 8</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eso</td>
<td>46 (41-52)</td>
<td>79 (76-84)</td>
<td>60 (54-67)</td>
<td>69 (65-73)</td>
</tr>
<tr>
<td>40 or 80 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>33 (22-44)</td>
<td>87 (81-93)</td>
<td>61 (45-76)</td>
<td>69 (61-76)</td>
</tr>
</tbody>
</table>

N = 1150  
Eso 40 mg QD or BID  
Europe, South America, Canada, Singapore

**Bottom Line** – One week of PPI therapy did not reliably identify responders at 8 weeks

_Talley et al. Aliment Pharmacol Ther 2007;26:673_
Which factors predict response to PPI therapy in FD?

- Patients with reflux symptoms more likely to respond to PPI therapy\(^1\)

- Patients with dysmotility symptoms are less likely to improve with PPI therapy\(^1\)
  - Case control studies suggest nausea\(^2\) and bloating/IBS symptoms\(^3,4\) are negative predictors of PPI response

\(^1\)Talley APT 1998;12:1055
\(^2\)Meineche-Schmidt Am J Gastro 2000;95:2777
\(^3\)Bolling-Sternevald Aliment Pharmacol Ther 2003;18:117
\(^4\)Meineche-Schmidt Aliment Pharmacol Ther 2011;33:41
### Pocket Chart for Calculation of therapeutic index to predict response to PPI

<table>
<thead>
<tr>
<th>Presence of symptom</th>
<th>Yes</th>
<th>No</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bothersome heartburn</td>
<td>+19</td>
<td>+9</td>
<td></td>
</tr>
<tr>
<td>Early satiety</td>
<td>+12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dull pain quality</td>
<td>-14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pain relieved by bowel movement</td>
<td>-13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nausea in women</td>
<td>-9</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Sum of points =**

**Therapeutic index (TI) = Sum of points multiplied by 0.1 =**

**Interpretation:**
- TI > 2: excellent response to esomeprazole;
- TI 1-2: good response to esomeprazole;
- TI 0-1: fair response to esomeprazole;
- TI < 0: no or little response to esomeprazole

Analysis of 805 primary care patients with upper GI symptoms

Buyer Beware: Do PPIs Cause Dyspeptic Symptoms?

- 120 *healthy volunteers* randomized to
  - Esomeprazole 40mg/d x 8 weeks followed by 4 weeks of placebo
  OR Placebo for 12 weeks
- GSRS completed weekly
  - Score>2 for heartburn, regurgitation or dyspepsia considered significant
- PPI group had significantly higher symptom scores at weeks 10, 11, 12 (p ≤ 0.023)
- PPI group more likely to have significant symptoms than placebo (week 12: 22% vs. 2%, p = 0.001)
- **Bottom line:** PPI withdrawal may lead to UGI symptoms possibly via rebound acid hypersecretion

*Reimer et al. Gastroenterol 2009;137:80*
How does abnormal gastric physiology contribute to Upper GI Symptoms?
Dyspeptic symptoms and meal-related pathophysiologic mechanisms

- **23%** Delayed gastric emptying: nausea, vomiting, and post-prandial fullness
- **35%** Hypersensitivity to gastric distension: pain, belching, and weight loss
- **40%** Impaired accommodation: early satiety, and weight loss

_Tack et al, Gastroenterology 2004; 127: 1239_
### Types of prokinetics

<table>
<thead>
<tr>
<th></th>
<th>Metoclopramide</th>
<th>Domperidone</th>
<th>Cisapride</th>
<th>Erythromycin ABT-229</th>
<th>Itopride</th>
<th>Tegaserod</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine-2 antagonist</strong></td>
<td>+</td>
<td>++</td>
<td></td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>5-HT₄ agonist</strong></td>
<td>+</td>
<td>++</td>
<td></td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>5-HT₃ antagonist</strong></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Motilin receptor agonist</strong></td>
<td></td>
<td></td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cholinesterase inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>QT prolongation</strong></td>
<td></td>
<td></td>
<td>++</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>
### Cochrane Meta-Analysis of Prokinetics for Functional Dyspepsia

- **19 RCTs (3178 patients)**

<table>
<thead>
<tr>
<th></th>
<th>% No or minimal symptoms</th>
<th>Therapeutic Gain (%)</th>
<th>NNT (95% CI)</th>
<th>RRR (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prokinetics</strong></td>
<td>57</td>
<td>10</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(5-12)</td>
<td>(18-45)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>47</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Significant assymetry by funnel plot*

*Moayyedi et al. Cochrane Collaboration 2007*
Dopaminergic Antagonists for Functional Dyspepsia
Metoclopramide for Functional Dyspepsia

- Dopaminergic and serotonergic antagonist
- Poor quality, older data suggests effects on gastric emptying
- No placebo controlled trials in FD
  - Less effective than cisapride
- Can prolong QT interval and increase prolactin
- CNS side effects in up to 20%
  - Anxiety, drowsiness, depression
  - Extrapyramidal side effects
  - Tardive dyskinesia

1 Perkel et al. Dig Dis Sci 1979; 24:662
2 Fumagalli and Hammer Scand J Gastroenterol 1994; 29:33
Domperidone for Functional Dyspepsia

- 9 double-blind studies (30-60 mg/day)
  - Peripheral dopaminergic antagonist
    - Reduced CNS side effects
  - Improvement in global assessment without clear effects on gastric emptying
  - Increases serum prolactin levels
    - Breast tenderness and galactorrhea in <5%
  - Can prolong QT interval
  - Not currently available in the US
Investigational Therapies for Functional Dyspepsia

- Antidepressants (SNRIs)
- Muscarinic antagonists
- 5-HT$_3$ antagonists
- Selective opioid agonists and antagonists
- Somatostatin analogs
- Capsaicin
- CCK antagonists
- CRF antagonists
- Neurokinin antagonists
- Ghrelin antagonists
Psychopharmacological Therapies for Functional Dyspepsia
Rationale for psychopharmacological therapy in functional dyspepsia

- Evidence of visceral hypersensitivity
- Increased psychosocial distress and history of abuse
- Overlap between functional GI disorders
- Effects of antidepressants on:
  - somatic and visceral pain
  - GI transit
Recent data on antidepressants for Functional Dyspepsia

- No effect of fluoxetine or paroxetine on sensation of gastric distention\(^1,2\)
  - Possible effect on accommodation

- In 25 non-depressed FD pts, flupenthixol & melitracen was more effective than placebo for global FD symptoms (74% vs. 26%, \(p=0.001\))\(^3\)

\(^1\)Tack et al. APT 2003;17:603
\(^2\)Ladabaum & Glidden. NGM 2002;14:395
\(^3\)Hanash et al. Gut 2007;56:A8-9
Venlafaxine for Functional Dyspepsia: Double-blind, Placebo-Controlled Trial

In a multicenter trial of 160 FD pts, venlafaxine was no more effective than placebo.
Treatment of Functional Dyspepsia

**Epigastric Pain**
- Antidepressant or behavioral therapy
- Test and treat *Hp*
- and/or empiric PPI

- Positive diagnosis
- Diet, lifestyle advice
- Reassure, OTC treatments
- Physician-patient relationship

Complimentary Therapies?
Treatment of Functional Dyspepsia

Epigastric Pain

- Test and treat Hp
- and/or Empiric PPI

Moderate

- Positive diagnosis
- Diet, lifestyle advice
- Reassure, OTC treatments
- Physician-patient relationship

Severe

Post-prandial distress

• Prokinetics
• Anti-emetics

Mild

Complimentary Therapies?

• Positive diagnosis
• Diet, lifestyle advice
• Reassure, OTC treatments
• Physician-patient relationship