Upper GI motility disorders and functional dyspepsia

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Functional Dyspepsia: Objectives

- Definition
- Epidemiology: natural history, and costs
- Etiology and pathophysiology
- Cost effective diagnosis
- Evidence-based treatments
- Future treatment options

Dyspepsia

- Persistent or recurrent abdominal pain or discomfort centered in the upper abdomen
- Uninvestigated dyspepsia following endoscopy
  - Organic: 30%
  - Functional: 70%

Symptoms of Functional Dyspepsia

- Epigastric pain/discomfort – 90%
- Post-prandial fullness – 75%
- Bloating – 75%
- Post-prandial nausea – 50%
- Early satiation – 50%
- Belching – 45%
- Weight loss – 30%
- Nausea and vomiting – 20%

Dyspepsia: Epidemiology and Burden of Illness

- Annual US prevalence = 20-25%
- Incidence is estimated at 1% per year
- Less than 50% of those with symptoms of dyspepsia seek medical care.
- Dyspepsia – 5% of all family practice consultations
- Dyspepsia significantly reduces quality of life
- Significant misconceptions abound – 20% believe their symptoms will turn into cancer

The Economics of Dyspepsia

- It is estimated that 10% of all healthcare expenditures in the United Kingdom go towards treating dyspepsia
- In the USA, direct costs (diagnostic studies, ER visits, medications) and indirect costs (absenteeism, presenteeism) for dyspepsia amount to more than $2 billion/year
- FD patients spend an average of $698/year treating their condition ($20 billion/year)
Functional Dyspepsia: Unclear Natural History

- 80% of patients have symptoms 18 to 24 months after diagnosis
- 74% of patients have symptoms 12 to 24 months later
- In contrast, some studies have shown 30-50% of patients experience resolution of symptoms over the course of 12 to 24 months

Functional Dyspepsia: Diagnosis

Rome III Criteria

- Presence of one or more of the following symptoms, thought to originate in the gastroduodenal region
  - Epigastric pain syndrome (EPS)
  - Epigastric burning
  - Postprandial distress syndrome (PDS): Meal-related FD
    - Bothering postprandial fullness after ordinary sized meals
    - Early satiety that prevents finishing a regular sized meal
- No evidence of structural disease to explain the symptoms and symptoms present for the past 3 months, with onset at least 6 months before diagnosis.
- Heartburn should be excluded

Functional Dyspepsia: Diagnosis

- Thorough history and physical examination
- Evaluation for warning signs/features
  - Unintentional weight loss, anemia or dysphagia
  - History of NSAID use; recurrent vomiting
  - Previous GI bleeding or ulcer disease
  - Abnormal physical examination other than epigastric pain/discomfort
- High-prevalence or low-prevalence Helicobacter pylori area?
- Evaluation of the upper GI tract (EGD)

Overlap of GI motor and sensory disorders

- Patients may have more than one disorder

Putative mechanisms linked to functional dyspepsia

- Gastric dysrhythmias
- Gastric hypersensitivity
- Small bowel hypersensitivity
- Delayed gastric emptying or ural hypersensitivity
- H. pylori gastritis
- Acid sensitivity
- Small bowel dysmotility
- Failure of fundic relaxation to a meal
- Vagal neuropathy
- Psychological distress / CNS disturbances

**Candidate genotypes: FD**

- **GNB3 (825 CC genotype)**
- **GNB3 (TT homozygous)**
- **GNB3 (825T allele)**
- **SNPs (single nucleotide polymorphism)**
  - HTR2A
  - MAGI2
  - IL-9
  - IL-4R

**Genetic Predisposition**

**FD Symptoms (Mild)**

- Stress
- Inflammation
- Helicobacter pylori

**FD Symptoms (Severe)**

- Anxiety
- Somatization
- Depression

**Range of treatment options in FD**

- **Avoidance of NSAIDs**
- **Antisecretory agents**
  - Prokinetics
    - Metoclopramide
    - Domperidone
    - Prokinetic agonists
    - Cisapride (withdrawn)
    - Tegaserod
- **Antidepressants**
  - Antidepressant tricyclics
  - SSRIs
- **Antacids**
- **Lifestyle modification**
  - Reassurance and explanation
  - Dietary modification

**Current issues with treating functional dyspepsia**

- The range of treatment options reflects the uncertain pathogenesis of functional dyspepsia, the diversity of symptoms and the lack of satisfactory treatment\(^1\)
- There is a significant placebo response: 40–60%\(^2\)

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\(^2\) Van Zanten et al, Am J Gastroenterol 1996; 91: 660

**Dr. Drossman’s Ten Commandments**

1. Obtain the history through a non-directive, non-judgmental patient-centered interview
2. Conduct a careful examination and cost-efficient investigation
3. Determine how much the patient understands about the illness and his/her concerns

Drossman DA. Gastroenterology 2006; 130: 1377-1390

**Dr. Drossman’s Ten Commandments**

4. Provide a thorough explanation of the disorder that takes into consideration the patient’s beliefs
5. Identify and respond realistically to the patient’s expectations for improvement
6. When possible, provide a link between stressors and symptoms that are consistent with the patient’s beliefs
Dr. Drossman's Ten Commandments

7. Set consistent limits.
9. Make recommendations consistent with the patient's interests.
10. Establish a long-term relationship with a primary care provider.

Current Management of Functional Dyspepsia

• Test & Treat for H. pylori or EGD?
• Dietary changes
• Historical treatments
• H. pylori eradication
• Antisecretory therapy
• Prokinetics
• Serotonergic agents
• Antinociceptive agents
• Psychological therapies

Treatment Strategy: Test & Treat, Prompt Endoscopy, or Empiric Acid Suppression

• Test & Treat for H. pylori: for younger patients, those without warning signs, and those in a high prevalence H. pylori area
• Prompt endoscopy: for older patients, those with warning signs; and those in a low prevalence H. pylori area
• Empiric PPI: safe for younger patients without warning signs, may decrease need for EGD, may treat patients with occult reflux

FD & Diet

• Intraduodenal infusion of fat induces symptoms in FD patients but not health volunteers
• Small amounts of fat added to meals induces FD symptoms of bloating, fullness and nausea
• A high fat meal induces more symptoms than an isocaloric high carbohydrate meal
• Upper abdominal fullness and bloating was directly related to the amount of fat ingested

Treatment of Dyspepsia (circa 1892)

• “Replace digestive juices that are lacking
• Infusions of hydrochloric acid and ferments
• 90-100 drops at intervals of 15 minutes after meals”

Cochrane Collaboration Meta-Analysis of H. pylori Cure for Functional Dyspepsia

• 12 RCTs (2903 patients)
• Mean response rate
  – Placebo: 29% (range, 7%-51%)
  – H. pylori cure: 37% (range, 21%-62%)
• Relative risk of symptoms remaining
  – 0.91 (95% CI: 0.86-0.95)
• NNT = 15 (95% CI: 10-28)
• Second meta-analysis of 10 RCTs in patients with FD followed for 1 year after treatment of H. pylori did not show any benefit in resolution of dyspepsia symptoms compared with placebo
**Cochrane systematic review updated**  

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
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</thead>
<tbody>
<tr>
<td>Blum/Talley</td>
<td>0.92 (0.81,1.03)</td>
<td>13.2</td>
</tr>
<tr>
<td>McColl</td>
<td>0.85 (0.77,0.93)</td>
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</tr>
<tr>
<td>Koell</td>
<td>0.95 (0.81,1.11)</td>
<td>7.3</td>
</tr>
<tr>
<td>Talley(Orchid)</td>
<td>0.97 (0.85,1.11)</td>
<td>10.6</td>
</tr>
<tr>
<td>Mase</td>
<td>1.07 (0.86,1.34)</td>
<td>7.5</td>
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<tr>
<td>Koell</td>
<td>0.91 (0.70,1.18)</td>
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<tr>
<td>Gisbert</td>
<td>0.83 (0.68,1.00)</td>
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<tr>
<td>Frankish</td>
<td>0.86 (0.62,1.24)</td>
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<tr>
<td>Koekeman</td>
<td>0.91 (0.78,1.07)</td>
<td>6.3</td>
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<tr>
<td>Godschal</td>
<td>0.76 (0.40,1.46)</td>
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</tr>
<tr>
<td>Huo</td>
<td>0.60 (0.36,1.05)</td>
<td>3.7</td>
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</tbody>
</table>

Overall (95% CI) = 0.91 (0.86,0.96) p<0.0001
Heterogeneity χ²=7.4 (df=11) p=0.77

**Are the H. pylori “responders” forme fruste ulcer patients?**

- Hypothetical
- No convincing evidence that symptom subgroups or H. pylori virulence factors will identify responders
- Past/future ulcer patients?
- Duodenitis?

Xia et al. Aliment Pharmacol Ther 2003; 17: 1-9

**H₂RA therapy Forest plot**  

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
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<tbody>
<tr>
<td>Delattre 1985</td>
<td>0.53 (0.40,0.69)</td>
<td>11.0</td>
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<tr>
<td>Gotthard 1988</td>
<td>0.74 (0.53,1.04)</td>
<td>9.6</td>
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<tr>
<td>Hadi 1989</td>
<td>0.03 (0.00,0.42)</td>
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<tr>
<td>Hansen 1996</td>
<td>1.20 (0.88,1.64)</td>
<td>10.1</td>
</tr>
<tr>
<td>Kharat 1985</td>
<td>1.18 (0.92,1.53)</td>
<td>5.1</td>
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<tr>
<td>Vius 1992</td>
<td>0.56 (0.37,0.83)</td>
<td>9.3</td>
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<tr>
<td>Saunders 1985</td>
<td>0.50 (0.32,0.78)</td>
<td>7.8</td>
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<tr>
<td>Singal 1989</td>
<td>0.57 (0.32,0.98)</td>
<td>8.1</td>
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<tr>
<td>Obsiya 1996</td>
<td>1.00 (0.88,1.14)</td>
<td>13.5</td>
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<tr>
<td>Gitelstein 1986</td>
<td>0.78 (0.57,1.07)</td>
<td>13.0</td>
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<tr>
<td>Blum 2000</td>
<td>0.69 (0.49,0.98)</td>
<td>13.6</td>
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Overall (95% CI) = 0.78 (0.65,0.93) p=0.0001

**H₂RAs for Functional Dyspepsia**

- Meta-analysis (2001)
- 22 RCTs in patients with nonulcer dyspepsia
- 14 studies: parallel groups; 8 studies: crossover
- 15 of 22 studies found H₂RA superior to placebo at relieving epigastric pain but not global symptoms of dyspepsia
- Significant design flaws in many studies, including crossover design and inclusion of GERD-predominant patients

**Cochrane Collaboration Meta-Analysis of PPI Therapy for Functional Dyspepsia**

- 7 RCTs (3031 patients)
- PPI for 2 to 8 weeks was superior to placebo in relieving symptoms of non-ulcer dyspepsia
- Relative risk of symptoms remaining – 0.86 (95% CI: 0.80-0.93)
- NNT = 9 (95% CI: 6-26)
- Six RCTs (2032 patients) found no difference between low-dose and standard-dose PPI for FD

**PPI therapy in Functional Dyspepsia**

- n=1262
  - Omeprazole 20 mg
  - Omeprazole 10 mg
  - Placebo
  - * p<0.05 vs placebo

**Prokinetic Agents for the Treatment of Functional Dyspepsia**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Primary mode of action</th>
<th>Antiemetic</th>
<th>Gastric Emptying</th>
<th>Visceral Sensitivity</th>
<th>Gastric Antral Motility</th>
<th>Gastric Fundic Accommodation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide</td>
<td>Dopamine antagonist</td>
<td>√</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Domperidone</td>
<td>Dopamine antagonist</td>
<td>√</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Tegaserod</td>
<td>5-HT4 agonist</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Levosulpiride</td>
<td>Dopamine antagonist 5-HT4 agonist</td>
<td>√</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

**Evidence for Prokinetic Therapies**

- **Cisapride** – 17 studies. Earlier apparent favorable response might have been attributed to publication bias. Recent review – no significant benefit compared with placebo.
- **Metoclopramide** – The most commonly used prokinetic in FD treatment. Recent meta-analysis failed to show any significant benefit above placebo.

**Evidence for Prokinetic Therapies**

- **Domperidone** – 8 studies were evaluated. Many had severe design flaws. Recent meta-analysis showed a slight benefit at improving symptoms compared with placebo.
- **Levosulpiride** – Dopamine antagonist not available in the USA. Recent study showed benefit compared with cisapride, though no placebo group was included.
Therapy in functional dyspepsia?

- Targets wrong?
  - Acid suppression
  - Requires altering multiple targets e.g. acid and motility/sensation
- Target the brain to get the gain?

CNS Dysfunction in FD

- Exaggerated prolactin response to buspirone in NUD
- Differences most significant at 90 min following the challenge.
- Female subjects, both patients and healthy volunteers, showed a greater response to buspirone than male subjects
  - ? Hypersensitivity of central serotonin receptors or secondary to chronic pain

Chua et al. BMJ 1992;305:280-282

Drug Effects on the CNS-Enteric Nervous System

Cortex
Spinal Cord
  - Descending inhibitory fibers
  - ANS input
  - 2nd order neurons
  - Dorsal horn nucleus
Dorsal root ganglion
Sensory nerve endings in gut

Functional Dyspepsia: TCAs

- Tricyclic antidepressants (TCAs)
  - Visceral and somatic perception are improved
  - Amitriptyline improved symptoms but did not alter sensation of gastric distention
  - Meta-analysis in patients with FGID found improvement of global symptoms (OR=4.2; NNT=3.2) and pain

Functional Dyspepsia: SSRIs/SNRIs

- Selective serotonin reuptake inhibitors (SSRIs)
  - Paroxetine enhanced gastric accommodation in healthy volunteers
  - Venlafaxine was no better than placebo
  - Mianserin or mirtazapine may be better choices
  - NIH Functional Dyspepsia Trial in progress (TCA vs. SSRI vs. placebo)
Emerging Therapies for Functional Dyspepsia

- Dopaminergic agents
- Serotonergic agents
- Kappa-opioid agents
- Antidepressants
- Ghrelin
- Behavioral therapy
- CAM
  - Capsaicin
  - Herbs

**Glass Half-empty**

- Dopamine receptor antagonists
  - Itopride
- Serotonergic agents
  - 5-HT4 receptor agonists (tegaserod)
  - 5-HT3 receptor antagonists (alosetron)
- Kappa-opioid agonists
  - Asimadoline
- Antidepressants
  - Venlafaxine

**Glass Half-full**

- TCAs & SSRI/SNRIs
- 5-HT1 agonists
- Acotiamide
- CAM
  - Iberogast
  - Capsaicin
  - Acupuncture
- Behavioral therapy
  - CBT
  - Hypnotherapy

**FD: 5-HT1A agonists**

- Tandospirone
  - DB, R, Placebo-controlled: Rome II criteria
  - N=144; 4 weeks: 10mg tid vs. placebo
  - Tandospirone improved symptoms of upper abdominal pain (p=0.02) and discomfort (p=0.002) more than placebo
- R-137696
  - DB, R, Placebo-controlled: Rome II criteria
  - N=53; 4 weeks: 2mg tid vs. placebo
  - No difference between drug and placebo

**Is the glass half-empty or half-full?**

Meta-Analysis of Antidepressants for IBS/NUD

<table>
<thead>
<tr>
<th></th>
<th>Favours Placebo</th>
<th>Favours Treatment</th>
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<tbody>
<tr>
<td>Greenbaum (1987)</td>
<td></td>
<td></td>
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<tr>
<td>Heffner (1978)</td>
<td></td>
<td></td>
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<tr>
<td>Loldrup (1989)</td>
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<tr>
<td>Mertz (1998)</td>
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<tr>
<td>Myers (1984)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rajagopalan (1998)</td>
<td></td>
<td></td>
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<tr>
<td>Steinhardt (1981)</td>
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<td>Tanum (1996)</td>
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Overall (95% CI) 0.9 (0.6-1.2)

Effects of antidepressant medications on abdominal pain scores


**emerging therapies for functional dyspepsia**

- Dopaminergic agents
- Serotonergic agents
- Kappa-opioid agents
- Antidepressants
- Ghrelin
- Behavioral therapy
- CAM
  - Capsaicin
  - Herbs

**glass half-empty**

- Dopamine receptor antagonists
  - Itopride
- Serotonergic agents
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  - 5-HT3 receptor antagonists (alosetron)
- Kappa-opioid agonists
  - Asimadoline
- Antidepressants
  - Venlafaxine

**glass half-full**

- TCAs & SSRI/SNRIs
- 5-HT1 agonists
- Acotiamide
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  - No difference between drug and placebo
FD: Acotiamide

- Enhances ACh release – blocks M1 & M2 receptors
- Inhibits AChE activity
- Phase IIa, R, DB; placebo-controlled trial
- N=71
- 100-300mg tid
- Significantly improved gastric accommodation and bloating

FD: Herbal remedies

- 17 RCTs were included in a systematic review (8 trials had a Jadad score >3)
- Peppermint and caraway oil were the best-studied herbal remedies
  - 4 RCTs showed their benefits
- Most studies were conducted with combinations
  - Effective ingredient and quality control were unclear
- Iberogast®, a combination of 9 herbs, relieved symptoms compared with placebo in several European studies
- Capsaicin – beneficial in small DB, R, placebo-controlled study; N=30.

FD: Acupuncture

- 68 patients with FD (Rome II criteria); randomized
- Mean age 35; 79% women
- 6-point acupuncture vs. nondefined point
- 3 sessions/week for 2 weeks
- Nepean Dyspepsia Index pre- and post-Tx
- Results: Both groups showed significant improvement in QOL and symptom scores (p<0.001), but no difference between the groups

Hypnotherapy in functional dyspepsia

Calvert et al. Gastroenterology 2002;123:1778–85

FD: Potential Future Therapies

- Mianserin (tetracyclic antidepressants)
- Mirtazapine (Remeron)
- Ghrelin
- Neurokinin antagonists
- Corticotrophin-releasing factor (CRF) antagonists
- Opioid antagonists

Functional Dyspepsia: Summary

- Antisecretory therapy is effective in a small subset of patients
- The benefits of H. pylori cure are small
- Small, frequent low-fat meals improve symptoms
- Effective pro-kinetic therapy is eagerly awaited
Functional Dyspepsia: Summary

- Agents that improve accommodation (i.e. tandospirone) and nociception are needed
- Treat co-existing anxiety
- Psychological therapies (TCAs and SSRIs) appear effective in a subset of FD patients
- Consider behavioral therapy (CBT) and/or hypnotherapy
- Complementary strategies require further study