Management of Functional Dyspepsia (FD)

Amy S. Oxentenko, MD, FACG
Program Director and Associate Chair, IM
Associate Professor of Medicine
Mayo Clinic, Rochester

Outline

• Define functional dyspepsia (FD) and subsets

• Describe the proposed mechanisms behind FD

• Compare the efficacy of lifestyle modifications, anti-secretory therapy, H. pylori treatment, prokinetics, psychotropic medications and complementary therapies for FD management
Dyspepsia

Secondary dyspepsia
Organic, systemic or metabolic cause identified

Functional dyspepsia
No identifiable cause found by traditional testing

Rome III to Rome IV: Functional Dyspepsia

• FD remains umbrella term
• Subcategories:
  ➢ Postprandial nature
  ➢ Epigastric distress
• Threshold for severity and frequency clarified
  • “Bothersome” = Severe enough to impact activities
  • Often ≥2 on a 5-point scale
• Frequency of symptoms not detailed in Rome III
  • Cutoffs created based on data such that no greater than 5% population would experience the same

**Definition of Functional Dyspepsia**

- Characterized by **1 or more** of the following:
  - Post-prandial fullness
  - Early satiation
  - Epigastric pain
  - Epigastric burning
- No evidence of structural disease (including EGD) that is likely to explain symptoms
- Fulfilled for the last 3 months with symptom onset at least 6 months before the diagnosis
- Must fulfill criteria for postprandial distress syndrome or epigastric pain syndrome


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**2 Subcategories of FD**

- **Post-prandial distress syndrome (PDS)**
  - Must include **1 or both** of the following at least 3 days per week:
    1. *Bothersome postprandial fullness*
       - Impacts usual activities
    2. *Bothersome early satiation*
       - Prevents finishing regular meal

- **Epigastric pain syndrome (EPS)**
  - Must include at least **1 of the following symptoms** at least 1 day per week:
    1. *Bothersome epigastric pain*
    2. *Bothersome epigastric burning*

PDS and EPS: Other Notes

- Additional sx may be present:
  - Bloating, belching, nausea
- Vomiting warrants a look for other causes
- Heartburn excluded as a dyspeptic symptom, but may coexist; same with GERD or IBS
- If symptoms relieved after flatus/stool, this shouldn’t be attributed to dyspepsia
- EPS pain doesn’t fulfill biliary pain criteria


Impact on Patients with FD

- Reduced QOL
- Increased distress
- Increased $$ burden
  - Medical bills
  - Loss of wages

Proposed Mechanisms of Functional Dyspepsia

- Infection
- Inflammation
- Gastroesophageal reflux
- Visceral hypersensitivity
- Altered accommodation
- Altered gastric emptying
- CNS modulation


Symptoms suggesting upper GI involvement

- Hx/Exam
- EGD
- Alarm Features?
  - YES
  - NO
- PPI Trial
  - YES
  - NO
- HP testing
- Sxs Resolve?
  - YES
  - NO
- Response?
  - YES
  - NO
- Continue PPI
- 2° Dyspepsia

Lifestyle Modifications in FD

• What do we tell our patients to do?
  • Avoid caffeine, alcohol and NSAIDs
  • Avoid high fat or high caloric foods
  • Eat small, more frequent meals

• Very few get improvement with this alone

• Other data:
  • Fats, not carbs, cause symptoms
  • Fullness/bloating related to fat ingestion and intraduodenal fat infusion\(^1\)\(^-\)\(^3\)
  • Others found no difference vs controls\(^4\),\(^5\)

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Anti-Secretory Therapy: H2RA

• Cochrane database meta-analysis

• 12 RCTs (H2RA vs placebo)
  • 2183 pts; NOT defined as FD by Rome III
  • Significant heterogeneity
  • Patients with GERD likely included

<table>
<thead>
<tr>
<th></th>
<th>H2RA Response (improvement)</th>
<th>Placebo response (improvement)</th>
<th>Gain</th>
<th>RRR</th>
<th>95% CI</th>
<th>NNT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>54%</td>
<td>40%</td>
<td>14%</td>
<td>23%</td>
<td>8-35%</td>
<td>7</td>
<td>5-21%</td>
<td></td>
</tr>
</tbody>
</table>

• 5 other RCTs found only epigastric pain and fullness improved with H2RA

# Anti-Secretory Therapy: PPI

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DRUG</th>
<th>BENEFIT</th>
<th>OF NOTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talley et al</td>
<td>Omeprazole 10-20 mg QD X 4 weeks</td>
<td>YES</td>
<td>No benefit in those with dysmotility</td>
</tr>
<tr>
<td>Wong et al</td>
<td>Lansoprazole 15-30 mg QD x 4 weeks</td>
<td>NO</td>
<td>Chinese pts; placebo pts had more benefit</td>
</tr>
<tr>
<td>Peura et al</td>
<td>Lansoprazole 15-30 mg QD x 8 weeks</td>
<td>SOME</td>
<td>HB predominant excluded; some HB more response</td>
</tr>
<tr>
<td>Van Zanten et al</td>
<td>Esomeprazole 40 mg QD X 8 weeks</td>
<td>NO</td>
<td>Those with HB or regurgitation excluded</td>
</tr>
<tr>
<td>Van Rensburg et al</td>
<td>Pantoprazole 20 mg QD X 4 weeks</td>
<td>YES</td>
<td>Study confined to those with &quot;ulcer-like symptoms&quot;</td>
</tr>
<tr>
<td>Talley et al</td>
<td>Esomeprazole 80 mg QD X 1 week</td>
<td>NO</td>
<td>Looked at sx response at 8 weeks</td>
</tr>
</tbody>
</table>

- Meta-analysis of RCTs
- 7 studies
  - 3725 pts
  - PPI superior to placebo
    - NNT 14.6
  - Benefit confined to those with:
    - Ulcer-like pain
    - Reflux-like dyspepsia
  - No benefit for those with:
    - Dysmotility-like features
    - Unspecified dyspepsia

**H. pylori Treatment in FD**

- Cochrane database meta-analysis
- 21 RCTs (HP eradication and FD sx)
  - 17 trials (3566 pts) grouped with dichotomous data and lack of heterogeneity
- HP eradication vs placebo or PPI

<table>
<thead>
<tr>
<th>HP group Response (improvement)</th>
<th>Placebo response (improvement)</th>
<th>Gain</th>
<th>RRR</th>
<th>95% CI</th>
<th>NNT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>36%</td>
<td>29%</td>
<td>7%</td>
<td>10%</td>
<td>6-14%</td>
<td>14</td>
<td>10-25%</td>
</tr>
</tbody>
</table>

- 12/17 did not show significant benefit


**H. pylori Eradication**

- 195 Chinese pts with FD (Rome III)$^1$
  - Improvement in epigastric pain/burning
    - *H. pylori* tx improvement 60.8-65.7%
    - Placebo improvement 31.8-33.3%
    - p<0.05

- 404 Brazilian pts with FD (Rome III)$^2$
  - Improvement in symptoms
    - PPI + 2 antibiotic improvement 50%
    - Daily PPI improvement 37%
    - p=0.01

Prokinetic Therapy in FD

- Cochrane database meta-analysis
- 19 RCTs with 3178 patients grouped with dichotomous data
  - Prokinetic (cisapride > domperidone) vs placebo

<table>
<thead>
<tr>
<th>Prokinetic Response (improvement)</th>
<th>Placebo response (improvement)</th>
<th>Gain</th>
<th>RRR</th>
<th>95% CI</th>
<th>NNT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>57%</td>
<td>47%</td>
<td>10%</td>
<td>33%</td>
<td>18-45%</td>
<td>6</td>
<td>5-12%</td>
</tr>
</tbody>
</table>

- Small studies, ? skewed results


Prokinetic Agents

<table>
<thead>
<tr>
<th>DRUG</th>
<th>STUDY</th>
<th>BENEFIT</th>
<th>OF NOTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegaserod</td>
<td>Vakil N, et al</td>
<td>SMALL</td>
<td>Increase in days with relief by 4.6% vs placebo; better response if severe</td>
</tr>
<tr>
<td>5-HT₄ agonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itopride</td>
<td>Holtmann, et al</td>
<td>NO</td>
<td>Phase III data no better than placebo (excluded reflux); available in Japan</td>
</tr>
<tr>
<td>D₂ antag/CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mosapride</td>
<td>Hallerback, et al</td>
<td>NO</td>
<td>Available in Japan</td>
</tr>
<tr>
<td>5-HT₄ agonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Arts J, et al</td>
<td>NO</td>
<td>Small study</td>
</tr>
<tr>
<td>Motilin agonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABT-229</td>
<td>Talley, et al</td>
<td>NO</td>
<td>Worsened symptoms with high dose</td>
</tr>
<tr>
<td>Motilin agonist</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acotiamide

- Enhances acetylcholinesterase release
  - Muscarinic antagonist; cholinesterase inhibitor
  - Relaxes fundus, gastroprokinetic
- Multi-center, RCT, 892 Japanese pts with FD (and PDS)

Weekly improvement rate in overall treatment efficacy
NNT = 6

Weekly elimination rate for all 3 sxes
(fullness, bloating, satiety)
NNT = 16


Psychotropic Agents: Venlafaxine

- Venlafaxine XR (SNRI) vs placebo
- RCT, double-blind, placebo-controlled, multi-center trial
- 170 pts, intention–to-treat response

Psychotropic Agents: Buspirone

- A 5-hydroxytryptamine 1A receptor agonist
- RCT, double-blind, placebo-controlled crossover
- 17 pts; dosing 10 mg TID

![Graph showing Dyspepsia Severity Score](Tack J, et al. CGH 2012;10:1239-45.)

Buspirone: What Symptoms Improve?

![Graph showing symptom severity improvement](Tack J, et al. CGH 2012;10:1239-45.)
Psychotropic Agents: SSRIs

- Sertraline (SSRI) vs placebo
- Pilot study, RCT, double-blinded
- FD (Rome II), ethnic Chinese, normal EGD, HP negative
- 193 pts, intention-to-treat response
  - 43 (22%) drop out by week 8 (19 placebo, 24 SSRI)
  - 95.8% of drop outs in SSRI group by week 4
- Significant improvement in Hong Kong Dyspepsia Index at week 8 in SSRI vs placebo in PP but not ITT analysis
- No differences in subjective global symptom resolution


Psychotropic Agents: SSRIs and TCAs

- RCT, double-blind, placebo-controlled; 8 NA sites
- TCAs vs SSRIs vs placebo; % adequate relief ≥5 weeks

Psychotropic Agents: SSRIs/TCAs

• Those with ulcer-like FD more likely to report adequate relief with amitriptyline
  • OR = 3.1 [CI 1.1-9.0]

• Those with dysmotility-like FD did not respond differently


Psychotropic Agents: SSRIs/TCAs

• Those with delayed gastric emptying at baseline had lower odds of reporting adequate relief than subjects with normal emptying.
  • OR = 0.4 [CI 0.2-0.8]

Psychotropic Agents: SSRIs and TCAs

- Systematic review, meta-analysis
- 8 studies (2 RCTs, 2 cross-overs)

**ALL antidepressants**
- No difference
- RR 0.85 (95% 0.69-1.03)

**SSRIs ONLY**
- No difference
- RR 1.00 (95% 0.86-1.17)

**Tricyclic ONLY**
- Difference
- RR 0.76 (95% 0.62-0.94)
- P = 0.01
- NNT = 7

*Side effects significantly more common in antidepressant groups

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**CAM Therapies**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Contained</th>
<th>Details</th>
<th>Treatment Response</th>
<th>Placebo Response</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1STW 5-II</td>
<td>Bitter candy tuft, matricaria, peppermint caraway, licorice root, lemon balm</td>
<td>120 pts Rome I FD 20 drops TID 2 x 4 weeks</td>
<td>43.3% Complete relief</td>
<td>3.3% Complete relief</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>2STW 5</td>
<td>Iberis amara, angelica, chamomile, caraway, thistle, lemon balm, peppermint, celandin, licorice, alcohol</td>
<td>315 pts Rome II FD 20 drops TID x 8 weeks</td>
<td>GIS drop 6.9</td>
<td>GIS drop 5.9</td>
<td>P = 0.04</td>
</tr>
<tr>
<td>3STW 5</td>
<td>Same</td>
<td>103 pts Rome II FD 20 drops TID x 4 weeks</td>
<td>GIS drop 6.6</td>
<td>GIS drop 4.5</td>
<td>P = 0.03</td>
</tr>
</tbody>
</table>

Take-Home Points

• **Lifestyle modifications:**
  - Often advised, but effect may be small and not used in isolation (adjunctive)
  - Lower fat, smaller meals suggested

• **Anti-secretory therapy:**
  - H2RA may be of benefit, with small effect, and may be better in those with pain (EPS)
  - PPIs may have modest benefit; may be better in those with pain or heartburn (EPS, not PDS)
  - PPIs are needed for >1 week to assess effect, but should be stopped after 4-8 weeks in non-responders

Take-Home Points

• *Helicobacter pylori* treatment:
  - There is improvement in some patients with dyspepsia when given *H. pylori* treatment
  - Approach dependent on prevalence of *H. pylori* infection

• **Prokinetic therapy:**
  - Prokinetics, while appealing for their gastric emptying features, show underwhelming results
  - Meta-analysis suggests benefit, but results largely based on cisapride and small studies
  - Other prokinetic drugs have not shown same beneficial results (need to consider harm)
  - Acotiamide looks promising as it relates to overall dyspepsia symptoms, particularly with PDS features
Take-Home Points

• **Psychotropic therapy:**
  • SSRIs likely of no benefit; SNRIs likely of no benefit
  • Buspirone may be of benefit for fullness, bloating, belching and nausea (PDS-like), but not in those with pain or burning (EPS-like)
  • TCAs (amitriptyline) may be of benefit in those with ulcer-type pain (EPS-like) and normal gastric emptying, but not in those with dysmotility-like features

• **Complementary therapy:**
  • STW 5 does show promising results as it relates to improvement in GI symptom scores

Thank you!

Oxentenko.amy@mayo.edu