Management of Dyspepsia

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Management Functional Dyspepsia

Objective:
• To update the criteria for diagnosis of functional dyspepsia (FD)
• To tell current management for functional dyspepsia
• To summarize Thai and Asian guidelines for functional dyspepsia
ACG Definitions of Dyspepsia

• Dyspepsia = “bad digestion” in Greek
• Chronic or recurrent pain or discomfort centered in the upper abdomen
  – Discomfort: a subjective negative feeling that is nonpainful, and can incorporate a variety of symptoms including early satiety or upper abdominal fullness

Rome III definition of Dyspepsia and Functional dyspepsia

Dyspepsia

- Gastro-esophageal reflux disease
- Irritable bowel syndrome

Uninvestigated

Organic
- Peptic ulcer
- Reflux esophagitis
- Gastric cancer

Investigated

Functional or NUD 60-90%
- Postprandial distress syndrome
- Epigastric pain syndrome

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

   • Postprandial distress syndrome
   • Epigastric pain syndrome

   **AND**

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

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

Tack, Tally, Camilleri et al. Gastroenterol 2006;130:1466
Rome III: diagnostic Criteria* for Postprandial Distress Syndrome

Must include one or both of the following:
1. Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week
2. Early satiation that prevents finishing a regular meal, at least several times per week

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

Supportive criteria
1. Upper abdominal bloating or postprandial nausea or excessive belching can be present
2. EPS may coexist

Tack, Tally, Camilleri et al. Gastroenterol 2006;130:1466
Rome III: diagnostic Criteria* for Epigastric Pain Syndrome

Must include all of the following:

1. Pain or burning localized to the epigastrium of at least moderate severity at least once/week
2. The pain is intermittent
3. Not generalized or localized to other abdominal or chest regions
4. Not relieved by defecation or passage of flatus
5. Not fulfilling criteria for gallbladder and SO disorders

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

Supportive criteria

• The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting
• Postprandial distress syndrome may coexist

Tack, Tally, Camilleri et al. Gastroenterol 2006;130:1466
Rome III
Functional Dyspepsia

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

Postprandial distress syndrome (PDS):
- Meal-related FD
- Postprandial heaviness or fullness
FD - Pathophysiological Mechanisms

- Neurohormonal dysfunction
- Genetic susceptibility
- Psychological factors/stress
- Poor sleep
- Infection
- Helicobacter pylori
- Eosinophilic duodenitis

Visceral hypersensitivity
- Gastroduodenal sensitivity
- Acid sensitivity

GIT motility disorders
- Gastric emptying
- Gastric accommodation
- CNS/autonomic dysregulation
Functional Dyspepsia
Abnormal Fundic Relaxation in Response to Meal

Dyspepsia: 40%

Functional dyspepsia pathophysiology

1/3 Impaired accommodation
Functional dyspepsia with early satiety and weight loss

1/3 Delayed gastric emptying
Functional dyspepsia but symptom associations controversial (nausea, vomiting and postprandial fullness)

1/3 Hypersensitivity to gastric distention
Functional dyspepsia with pain, belching and weight loss

### Pathophysiology of Functional Dyspepsia: Therapeutic Implications

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Presentations</th>
<th>Established RX.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed gastric emptying</td>
<td>Dyspepsia with postprandial fullness, nausea and vomiting</td>
<td>Prokinetic</td>
</tr>
<tr>
<td>Hypersensitivity to gastric distention</td>
<td>Dyspepsia with postprandial pain, belching</td>
<td>Visceral analgesic therapy: TCA, Prokinetic, tegaserod</td>
</tr>
<tr>
<td>Impaired postprandial fundus relaxation</td>
<td>Dyspepsia with early satiety and weight loss</td>
<td>Fundus relaxing therapy: Prokinetic, tegaserod, SSRI</td>
</tr>
<tr>
<td>Acid-related or hypersensitivity</td>
<td>Dyspepsia with postprandial pain, nausea</td>
<td>Acid-suppressive therapy: PPI, H2RA</td>
</tr>
</tbody>
</table>
Dietary and lifestyle modifications for patients with FD

- Smaller, more frequent meals
- A low fat diet
- Avoid irritating foodstuffs
- Stop smoking
- Reduce alcohol
- Reduce caffeine
- Avoid carbonated drinks
- Avoid NSAID use
- Reduce stress, more relax
Diet and FD

- Majority of individuals report induction or worsening of symptoms after meal ingestion
- Specific foods and macronutrients and other dietary habits to the induction and/or exacerbation of dyspeptic symptoms has been poorly studied
- Fullness and bloating were directly related to the amount of fat ingested, while only fullness was inversely related to the amount of carbohydrate ingested

Lacy BE, et al. APT 2012;36:3-15
Placebo response in functional dyspepsia

30%-60%

This indicates that many patients will not required at all, and would be benefit most from general advice and reassurance
Efficacy of pharmacological therapy for uninvestigated dyspepsia

Cochrane Review 2002
PPI vs antacids, n=1186
  RR=0.72 (95%CI, 0.64-0.80)
PPI vs H₂RA, n=1267
  RR=0.64 (95%CI, 0.49-0.82)
PPI vs cisapride, FU 8,14,52 wks
  RR=0.95 (95%CI, 0.80-1.13)
H₂RA vs antacids, RR=0.86 (95%CI, 0.35-2.11)

Conclusion: PPI is significantly better than H₂RA and antacids
Pharmacological interventions for functional dyspepsia

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>RRR</th>
<th>95% CI</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prokinetics</td>
<td>33%*</td>
<td>18%-45%</td>
<td>4</td>
</tr>
<tr>
<td>(n=3178)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂RA (n=2,183)</td>
<td>23%*</td>
<td>8%-35%</td>
<td>8</td>
</tr>
<tr>
<td>PPIs (n=3347)</td>
<td>13%*</td>
<td>4%-20%</td>
<td>9</td>
</tr>
<tr>
<td>Antacid (n=109)</td>
<td>-2%#</td>
<td>-36%-24%</td>
<td>-</td>
</tr>
<tr>
<td>Sucralfate (n=246)</td>
<td>29%#</td>
<td>-40%-36%</td>
<td>-</td>
</tr>
</tbody>
</table>

* significant more effective than placebo
# not statistically significant superior to placebo
\textsuperscript{t} publication bias

Moayyedi et al. Cochrane Database Syst Rev. 2007
Symptom subgroup on efficacy of PPI therapy in FD

Patient subgroup

- Reflux group: 0.75 (0.66, 0.88)
- Epigastric pain group: 0.85 (0.79, 0.92)
- Dysmotility group: 1.02 (0.92, 1.13)

Overall (95% CI): 0.87 (0.82, 0.92)

Risk ratio: 1.55

Favors PPI therapy
Favors placebo

Moayyedi P and et al. Gastroenterology 2004
Antisecretory Drugs in FD

• H₂RA
  – Epigastric pain (RRR = 19%; 95% CI = 4–32) and postprandial fullness (RRR = 29%; 95% CI = 0–49) were improved by H₂RA therapy compared with placebo

• PPIs
  1. PPI BID improved a small but statistically significant benefit in a per protocol BUT not in an ITT*
  2. BID PPI (esomeprazole 80 mg) for 1 wk → little value in predicting symptom response at 8 wks**

**Talley NJ, et al. APT 2007;26:673-82
Prokinetics

- Metoclopramide (Plasil)
- Cisapride (Prepulsid)
- Domperidone (Motilium-M)
- Itopride (Ganaton)
- Mosapride (Gasmotin)
- Prucalopride (Resolor)
- Tegazerod (Zelmac)
- Erythromycin
Prokinetics – Action Mechanism

Shinyaku to Rhinsho. 2001; 50(6): 617-624
## Prokinetic drugs

<table>
<thead>
<tr>
<th></th>
<th>Itopride</th>
<th>Cisapride</th>
<th>Mosapride</th>
<th>Metoclopramide</th>
<th>Domperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prokinetic</strong></td>
<td>strong</td>
<td>strong</td>
<td>strong</td>
<td>strong</td>
<td>moderate</td>
</tr>
<tr>
<td><strong>Antiemetic</strong></td>
<td>moderate</td>
<td>none</td>
<td>none</td>
<td>strong</td>
<td>Moderate to strong</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>FMO3</td>
<td>CYP 3A4</td>
<td>CYP 3A4</td>
<td>CYP 2A9</td>
<td>CYP 3A4</td>
</tr>
<tr>
<td><strong>Enzyme Pathway</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>QT-prolong</strong></td>
<td>-</td>
<td>++</td>
<td>?</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Prolactin</strong></td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>rare-moderate</td>
<td>rare-moderate</td>
</tr>
<tr>
<td><strong>elevation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Extrapyramidal</strong></td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Frequent</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Mode of action</strong></td>
<td>D₂ receptor antagonist, 5HT₄ agonist</td>
<td>5HT₄ agonist</td>
<td>5HT₄ agonist</td>
<td>D₂, 5HT₄ agonist</td>
<td>D₂ antagonist</td>
</tr>
<tr>
<td></td>
<td>AChE inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cisapride and Domperidone for FD: A Meta-analysis

• **Cisapride**: 17 studies
  – partial 5-HT$_4$ agonist
  – improvement in global assessment, epigastric pain, early satiety, abdominal distention, nausea
  – unclear if accelerated gastric emptying accounts for clinical improvement

• **Domperidone**: 8 studies
  – peripheral dopamine antagonist
  – improvement in global assessment

Veldhuzen Am J Gastro 2001;96:689
A Placebo-Controlled Trial of Itopride in Functional Dyspepsia:
Response Rates Based on Patients’ Global Assessment of Efficacy

Holtmann G et al. NEJM 2006:354;832
Itopride vs Placebo Phase III, Multicenter, RCT

<table>
<thead>
<tr>
<th>Parameter Time point</th>
<th>Category</th>
<th>Placebo (N=261)</th>
<th>Itopride (N=264)</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Placebo (N=330)</th>
<th>Itopride (N=315)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPA</td>
<td>Responder N (%)</td>
<td>109 (41.8)</td>
<td>110 (41.7)</td>
<td>0.98</td>
<td>104 (31.5)</td>
<td>105 (33.5)</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>Non responder N (%)</td>
<td>152 (58.2)</td>
<td>154 (58.3)</td>
<td></td>
<td>226 (68.5)</td>
<td>210 (66.7)</td>
<td></td>
</tr>
<tr>
<td>LDQ questions 1 and 8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Responder N (%)</td>
<td>175 (67.0)</td>
<td>178 (67.4)</td>
<td>0.92</td>
<td>197 (59.7)</td>
<td>194 (61.6)</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>Non responder N (%)</td>
<td>86 (33.0)</td>
<td>86 (32.6)</td>
<td></td>
<td>133 (40.3)</td>
<td>121 (38.4)</td>
<td></td>
</tr>
<tr>
<td>LDQ questions 1 and 8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Responder N (%)</td>
<td>126 (48.3)</td>
<td>158 (59.8)</td>
<td>&lt;0.01</td>
<td>132 (40.0)</td>
<td>128 (40.6)</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>Non responder N (%)</td>
<td>135 (51.7)</td>
<td>106 (40.2)</td>
<td></td>
<td>198 (60.0)</td>
<td>187 (59.4)</td>
<td></td>
</tr>
</tbody>
</table>

- <sup>a</sup> p value from ac hi-square test  
- <sup>b</sup> imputation of missing values as non responder. Difference of 1 unit on LDQ pain and fullness  
- <sup>c</sup> imputation of missing values as non responder. Difference of 2 units on LDQ pain and fullness  
- GPA-Global patient assessment of efficacy  
- LDQ-Leeds dyspepsia questionnaire  
Meta-analysis of RCT in FD with Serotonin agonists

Mosapride has a 6.7% greater probability of producing a response compared with control agents (summary statistic: 0.067; 95% CI: 0.010–0.124; $P = 0.021$), whereas no significant effect is observed with cisapride.

### Change in the symptom score before and after the 4 weeks of Rebamipide (mean ± SD)

<table>
<thead>
<tr>
<th>Dyspepsia group</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>P-value (vs placebo)</th>
<th>P-value (vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptom score</td>
<td>P-value</td>
<td>Symptom score</td>
<td>P-value</td>
</tr>
<tr>
<td>Heartburn</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.33 ± 0.65</td>
<td>0.624</td>
<td>0.15 ± 0.36</td>
<td>0.058</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.43 ± 0.73</td>
<td></td>
<td>0.30 ± 0.66</td>
<td>0.096</td>
</tr>
<tr>
<td>Retrosternal discomfort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.52 ± 0.91</td>
<td>0.534</td>
<td>0.24 ± 0.50</td>
<td>0.020</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.51 ± 0.65</td>
<td></td>
<td>0.24 ± 0.60</td>
<td>0.012</td>
</tr>
<tr>
<td>Epigastric discomfort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.33 ± 0.96</td>
<td>0.059</td>
<td>0.94 ± 0.83</td>
<td>0.003</td>
</tr>
<tr>
<td>Treatment</td>
<td>1.70 ± 0.81</td>
<td></td>
<td>0.97 ± 0.87</td>
<td>0.000</td>
</tr>
<tr>
<td>Nausea vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.70 ± 0.92</td>
<td>0.431</td>
<td>0.39 ± 0.66</td>
<td>0.019</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.81 ± 0.91</td>
<td></td>
<td>0.49 ± 0.73</td>
<td>0.11</td>
</tr>
<tr>
<td>Bloating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.85 ± 1.00</td>
<td>0.115</td>
<td>0.76 ± 1.03</td>
<td>0.477</td>
</tr>
<tr>
<td>Treatment</td>
<td>1.24 ± 1.01</td>
<td></td>
<td>0.92 ± 0.95</td>
<td>0.038</td>
</tr>
<tr>
<td>Early satiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.03 ± 0.88</td>
<td>0.287</td>
<td>0.76 ± 0.79</td>
<td>0.680</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.84 ± 0.87</td>
<td></td>
<td>0.73 ± 0.87</td>
<td>0.356</td>
</tr>
<tr>
<td>Appetite loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.39 ± 0.70</td>
<td>0.741</td>
<td>0.39 ± 0.70</td>
<td>1.000</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.46 ± 0.77</td>
<td></td>
<td>0.38 ± 0.72</td>
<td>0.317</td>
</tr>
<tr>
<td>Belching</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.52 ± 0.83</td>
<td>0.283</td>
<td>0.47 ± 0.69</td>
<td>0.480</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.74 ± 0.92</td>
<td></td>
<td>0.45 ± 0.67</td>
<td>0.008</td>
</tr>
<tr>
<td>Morning discomfort</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Placebo</td>
<td>0.97 ± 1.19</td>
<td>0.576</td>
<td>0.61 ± 0.93</td>
<td>0.011</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.73 ± 0.84</td>
<td></td>
<td>0.70 ± 0.88</td>
<td>0.736</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.06 ± 1.03</td>
<td>0.495</td>
<td>0.70 ± 0.88</td>
<td>0.014</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.92 ± 0.98</td>
<td></td>
<td>0.65 ± 0.89</td>
<td>0.025</td>
</tr>
<tr>
<td>Pain or discomfort relieved after a meal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.48 ± 0.76</td>
<td>0.995</td>
<td>0.21 ± 0.53</td>
<td>0.070</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.47 ± 0.73</td>
<td></td>
<td>0.424</td>
<td>0.013</td>
</tr>
</tbody>
</table>
Effects of rebamipide on subjective reduction of symptoms. Symptoms were rated on an analog scale. Data were expressed by percent symptom reduction after therapy.
Eradication of *H. pylori* for functional dyspepsia

17 RCT, 3566 patients
Follow up 3-12 months
- Mean placebo response = 29%
- Mean eradication response = 36%
- RRR in *H. pylori* eradication compared to placebo = 10% (95% CI = 6%-14%)
- NNT to cure one case of dyspepsia = 14 (95% CI = 10-25)

If there is a benefit, it is limited to a subgroup of patients

Moayyedi et al. Cochrane Database Syst Rev. 2006
Eradication of \textit{H.pylori} for functional dyspepsia

- 195 Chinese FD patients (Rome III) with \textit{H. pylori} found that symptoms of
  - Epigastric pain and epigastric burning were more likely to improve compared to placebo (overall response rate 60.8–65.7\% vs. 33.3–31.8\% respectively; \( P < 0.05 \))

- 404 Brazilian FD pts (Rome III)
  - 49\% of pts treated with \textit{H pylori} eradication and F/U at 12 mos
  - 50\% improvement in symptoms vs 37\% of FD patients treated with a daily PPI (\( P = 0.01 \))

FUNCTIONAL DYSPESIA
Amitryptiline in functional dyspepsia

• A Japanese RCT
  • amitriptyline in FD patients who had failed an H₂RA or a prokinetic  → amitriptyline improved symptoms in 70% vs 20% of placebo


Anti-anxiety or Anti-depressants for FD: A systematic review

- 13 RCTs (1717 patients)
- 11/13 trials showed benefit
- 4 trials included in a formal statistical analysis
  - Manserin, levosulpiride, clidinium/diazepoxide
  - Funnel plot was asymmetrical - publication bias?

<table>
<thead>
<tr>
<th>Anti-depressants or anxiolytics</th>
<th>Anti-depressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>0.55</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.36-0.85)</td>
</tr>
</tbody>
</table>

Hojo, et al. J Gastroenterol 2005
Effects of SSRIs on gastric physiology

• 16 healthy volunteers treated with **paroxetine** 20 mg/d or placebo¹
  – No difference in gastric sensation
  – Paroxetine enhanced accommodation

• 10 healthy volunteers treated with **sertraline** 50 mg/d or placebo x 2 wks then crossed over²
  – No difference in gastric sensation or somatic plain (ice water immersion)

• No RCTs in FD pts

¹Tack et al, APT 2003
²Ladabaum & Gildden, NGM 2002
SSRIs and SNRIs for FD

- No effect of fluoxetine or paroxetine on sensation of gastric distention
  - 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)
- In a multicenter trial of 160 FD pts, venlafaxine (SNRI) was no more effective than placebo (23% vs 20%, p=0.70)

Tack et al, APT 2003
Ladabaum & Gildden, NGM 2002
Acotiamide

• Acotiamide
  – a muscarinic antagonist and cholinesterase inhibitor
  – A multicentre, randomised, PBCT in 892 Japanese FD patients with PDS
    • 52.2% acotiamide had a global improvement in FD symptoms vs 34.8% in the placebo group (P < 0.001)

Acotiamide in FD
Evaluation by real-time US

Buspirone: $5HT_{1A}$ receptor agonist

- DSS of before and after placebo was no significant (10.8 vs 9.5)
- In buspirone groups was significantly improved (11.5 vs 7.5; $p<0.005$)

Buspirone for FD

**Gastric emptying rates**

Table 2. Influence of Placebo and Buspirone on Different Parameters of Gastric Sensorimotor Function Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Variable</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Buspirone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric emptying rate</td>
<td>Solid emptying half-emptying time (min)</td>
<td>95 ± 16</td>
<td>88 ± 6</td>
<td>110 ± 17</td>
</tr>
<tr>
<td></td>
<td>Liquid emptying half-emptying time (min)</td>
<td>64 ± 5</td>
<td>80 ± 6</td>
<td>119 ± 24</td>
</tr>
<tr>
<td>Gastric barostat</td>
<td>MDP (mm Hg)</td>
<td>6.6 ± 0.6</td>
<td>7.1 ± 0.6</td>
<td>5.9 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>Fasting discomfort threshold (mm Hg above MDP)</td>
<td>5.5 ± 0.3</td>
<td>5.3 ± 0.5</td>
<td>5.9 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>Fasting discomfort volume (mL)</td>
<td>406 ± 21</td>
<td>367 ± 47</td>
<td>380 ± 25</td>
</tr>
<tr>
<td></td>
<td>Gastric accommodation (mL)</td>
<td>132 ± 40</td>
<td>141 ± 32</td>
<td>229 ± 28</td>
</tr>
<tr>
<td></td>
<td>Postprandial discomfort threshold (mm Hg above MDP)</td>
<td>8.6 ± 2.1</td>
<td>7.7 ± 1.3</td>
<td>6.4 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>Postprandial discomfort volume (mL)</td>
<td>523 ± 84</td>
<td>457 ± 54</td>
<td>593 ± 49</td>
</tr>
</tbody>
</table>

Buspirone did not alter the rate of gastric emptying of solid but delayed gastric emptying of liquid compare with baseline.

Meal-related symptom severity score

Total meal related symptom score were significantly lower in buspirone compared with baseline or placebo (67 vs 119).

Buspirone significantly improved for postprandial fullness, bloating, nausea, and belching; placebo improved only belching.

Anti-nociceptive agents

• Gabapentin
  – No data for FD

• Pregabalin
  – Post hoc analysis of data from six RCTs in patients with generalised anxiety disorder and prominent GI symptoms → pregabalin was significantly more effective than placebo in treating both anxiety and gastrointestinal symptoms

Lacy BE, et al. APT 2012;36:3-15
Bismuth in FD

<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>

**Sucralfate:**

RRR = 29%; 95% CI -40%, 62%

NOT statistically significant

---

Effect STW-5 on Gastric Physiology

Intragastric volume

*P<0.05 n=9
**P<0.05 n=12

No effect on antral or duodenal MI or solid phase GE

Pillchlwiez et al, Am J gastroenterol 2007
Complimentary Therapies for functional dyspepsia

- **STW 5 (Iberogast)** affects gastric motility and improve upper GI symptoms

- **Artichoke leaf extract** more effectively improve symptoms and QOL than placebo in pts with functional dyspepsia

- **Capsaisin** has been shown in small trials to improve epigastric pain and fullness

Iberogast is a tincture of the following herbs:
- German Chamomile (*Matricaria recutita*) flower
- Clown’s Mustard (*Brassica nigra*) plant
- Angelica (*Angelica archangelica*) root and rhizome
- Caraway (*Carum carvi*) fruit
- Lemon Balm (*Melissa officinalis*) leaf
- Celandine (*Chelidonium majus*) aerial part
- Licorice (*Glycyrrhiza glabra*) root
- Peppermint (*Mentha x piperita*) leaf

1 Honenester, NGM 2004
2 Melzer, APT 2004
3 Holffmann, APT 2003
4 Bortolotti, APT 2002
Herbal Remedies for FD: A Systematic Review

• 17 RCTs included
• 8 had a Jadad score > 3
• Peppermint not caraway oils most studied
  – 4 RCTs showed benefit
• Most studied done with combinations of herbs
  – Effective ingredients unclear
  – Questionable quality control

Psychological therapies for FD

- Cognitive-behavioral therapy
- Hypnotherapy
- Relaxations / Stress management
- Interpersonal therapy

Recent systematic review concluded that there is insufficient evidence to support the efficacy of psychological therapies in FD

Soo et al, Am J Gastroenterol 2004
Treatment algorithm for functional dyspepsia according to the Rome III classification

Dyspeptic symptoms

Endoscopy 70%

Functional dyspepsia
(erase if HP+)

Organic dyspepsia

Meal-related (PDS) Meal-unrelated (EPS)

Prokinetic Acid suppressive

Add or switch to acid suppressive Add or switch to prokinetic

Tricyclic agent if refractory

HP+, Helicobacter pylori-positive; PDS, postprandial distress syndrome; EPS, epigastric pain syndrome

Geeraerts B, Tack J. J Gastroenterol 2008
## Summary

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Therapeutic gain</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H pylori</em> eradication</td>
<td>6-14%</td>
</tr>
<tr>
<td>PPIs</td>
<td>7-10%</td>
</tr>
<tr>
<td>H$_2$RA</td>
<td>8-35%</td>
</tr>
<tr>
<td>Prokinetic agents</td>
<td>18-45%</td>
</tr>
<tr>
<td>TCAs</td>
<td>Response rates 64-70%</td>
</tr>
<tr>
<td>SNRIs</td>
<td>= placebo</td>
</tr>
</tbody>
</table>

Lacy BE, et al. APT 2012;36:3-15
Functional Dyspepsia

\[ H. pylori \text{ test and eradication, if not done before}\]

\[ \text{Dietary modifications}\]

\[ \text{Predominant symptom(s)}\]

Epigastric pain or burning

- Proton pump inhibitor with or without Prokinetic agent
  - Response after 4 or 8 weeks
    - Yes
      - Try anti-depressant or anxiolytic agent
      - Try herbal medication
  - No
    - No response
      - Refer to specialists
    - Try to discontinue or on demand treatment

Postprandial fullness, early satiation, upper abdominal bloating, nausea, vomiting or belching

- Prokinetic agent with or without Proton pump inhibitor
  - Response after 4 or 8 weeks
    - Yes
    - No

Proposed treatment algorithm for FD

Lacy BE, et al. APT 2012;36:3-15
Functional Dyspepsia-Rome III
Management algorithm

Functional Dyspepsia

- Postprandial distress syndrome (PDS)
  - Prokinetic drugs
  - Fundic relaxors

- Epigastric pain syndrome (EPS)
  - Acid suppressive therapy
  - H. Pylori eradication

- Psychotropic drugs
  - Psychotherapy / hypnotherapy

Talley NJ, AGA Post Graduate Course 2012
Functional Dyspepsia: Practical Management

• Check diagnosis:
  - Is it true FD?
  - Any overlapping disease?: GERD, IBS
  - Any alarm symptom?

• Starting with medication
  - PPI: single or combination with other medications
  - Prokinetic drug
  - TCA
  - Other medications or management in combination
  - Continuing follow up and look for patient’s concern
Functional Dyspepsia

- 15-40% respond to PPI
- 15-40% Hp positive FD patients respond to Hp eradication
- 15-40% respond to H2-blocker
- 15-40% respond to prokinetics
- 15-40% respond to placebo
- 15-40% respond to ..........

15-40% respond to ............