Management of Dyspepsia 2016

John K. DiBaise, MD, FACP
Professor of Medicine
Mayo Clinic in Arizona
dibaise.john@mayo.edu

Learning Objectives

• Identify causes and significance of dyspepsia
• Describe alarm features in dyspepsia warranting more aggressive evaluation
• Discuss a practical approach to the management of dyspepsia
What is Dyspepsia?

- Dys (Bad) Peptin (Digestion)
- ‘Indigestion’
- Constellation of symptoms thought to originate from the upper gastrointestinal tract
- Most commonly a functional etiology
- Tends to follow a relapsing-remitting course
- May be food-related (about 80%)

Epidemiology and Significance

- Prevalence of dyspepsia ranges from 20% to 40%
  - Accounts for about 5% of primary care visits
- Global prevalence of functional dyspepsia (FD) in the community ranges from 10-30%
  - Prevalence depends upon definition used (and whether GERD and IBS symptoms excluded)
  - Up to 40% consult a healthcare provider
- Natural history of FD not well characterized
  - About 50% remain symptomatic after 5-year follow-up
  - No evidence to suggest FD associated with decreased survival
- Reduces quality of life and contributes a significant economic burden
  - About $18 billion in 2009
  - Affects work attendance/productivity

Ford AC et al. Gut 2015
Lacy BE et al. APT 2013
Mahadeva S et al. WJG 2006
Risk Factors for Dyspepsia

- Female gender
- Increasing age
- High socioeconomic status
- Decreased urbanization
- *H. pylori* infection
- NSAID use
- Low educational level
- Renters
- Absence of central heating
- Sharing a bed with siblings
- Being married

Mahadeva S et al. WJG 2006
Shaib Y et al. AJG 2004

Causes of Dyspepsia

- Organic (examples)
  - Peptic ulcer disease (10%)
  - Gastroesophageal reflux disease
  - *Helicobacter pylori* (5%)
  - Gastric cancer (<1%)
  - Pancreaticobiliary disease
  - Gastric dysmotility
  - Medications
  - Parasites
  - Abdominal wall pain
  - Celiac disease (NOT increased)
- No cause found (>70%)
  - **Functional Dyspepsia**
  - Non-ulcer Dyspepsia
  - Idiopathic Dyspepsia

**Symptoms do not reliably distinguish between organic and functional dyspepsia**

Ford AC et al. CGH 2010
Ford AC et al. APT 2009
**Rome IV Criteria: Functional Dyspepsia**

Presence of **one or more** of the following symptoms thought to originate in the gastroduodenal region:

- Bothersome postprandial fullness
- Bothersome early satiation
- Bothersome epigastric pain
- Bothersome epigastric burning

No evidence of structural disease (EGD) to explain the symptoms.

Symptoms present during the last 3 months with onset at least 6 months before diagnosis.


---

**Rome IV FD Subtypes**

- **Postprandial distress syndrome**
  - Bothersome (i.e., severe enough to impact usual activities) postprandial fullness at least 3 days/week **and/or**
  - Bothersome early satiation at least 3 days/week
  - Supporting remarks
    - Postprandial epigastric pain/burning, bloating, nausea, excessive belching may be present
    - Vomiting warrants consideration of another disorder
    - Heartburn is not a dyspeptic symptom but may coexist
    - Symptoms that are relieved with defecation or passing flatus should generally not be considered part of FD
    - Other individual symptoms or groups of symptoms (e.g., GERD, IBS) may coexist with PDS

Rome IV FD Subtypes

- **Epigastric pain syndrome**
  - Bothersome (i.e., severe enough to impact usual activities) epigastric pain and/or burning at least once/week
  - **Supportive remarks**
    - Pain may be induced/relieved by eating but may occur while fasting
    - Postprandial epigastric bloating, belching and nausea can be present
    - Persistent vomiting suggests another disorder
    - Heartburn is not a dyspeptic symptom but may coexist
    - Symptoms that are relieved with defecation or passing flatus should generally not be considered part of FD
    - Other digestive symptoms (e.g., GERD, IBS) may coexist with EPS


Overlap of GI Symptoms in FD

- **‘Pure’ dyspepsia**
- Insufficient GI symptoms
- Other serious diagnoses

‘Pure’ dyspepsia: Patients without predominant GERD symptoms or symptoms of IBS
Highlights difficulty in recruiting patients with Rome II definition of dyspepsia

Vakil N et al. APT 2005
**Importance of the History in Dyspepsia**

- **Alarm symptoms/features**
  - Bleeding, persistent vomiting, dysphagia, weight loss, family h/o UGI neoplasm
  - Palpable abdominal mass or lymphadenopathy
  - Iron deficiency
  - **Alarm symptoms have only modest predictive capability**

- **Age**
  - New onset of symptoms after age 55 should prompt early EGD
  - Risk of malignancy in most US populations is <10/100,000 in those under age 55 (SEER database)
  - In those from a region of higher risk of gastric cancer, a younger age may be considered

- **NSAID use**

- **Diet/food history**

  Vakil N et al. Gastro 2006

---

**Functional Dyspepsia: Mechanistic Possibilities**

- **Symptoms correlate poorly with the physiologic abnormalities**

  - **CNS modulation**
    - Anxiety, stress, etc.

  - **Visceral hypersensitivity**
    - H+, wall distension, etc.

  - **Gastroesophageal reflux**
    - H+, bile acids, etc.

  - **Gastric inflammation**
    - *Bacteria-H. pylori*

  - **Duodenal inflammation**
    - H+, bacteria, viruses, allergy, etc.

  - **Decreased fundic accommodation**

  - **Abnormal distribution of gastric contents**

  - **Delayed emptying**

  - **Abnormal myoelectrical activity**

  - **Overdistended antrum**

  - **Intestinal dysmotility**

Initial Management of Dyspepsia

- Distinguish GERD from dyspepsia
- Exclude organic causes
- Obtain key history (alarm features, age, NSAID use)
- Identify relationship of symptoms to food intake and specific food items
- Provide reassurance and education
- Consider pharmacotherapies and other therapies based upon specific symptoms and their severity

Role of Diet Modification in FD

- Based on observation that nutrient intake modules upper GI sensorimotor function and likely also influences symptoms
  - Likely that patients modify their diet habits to minimize symptoms
- Contribution of specific foods and other dietary habits has been poorly studied
  - Conflicting results
- FD pts more often experience symptoms after intraduodenal fat infusion
- Smaller meals and reduced fat intake are promising targets but require more rigorous study

Lacy BE et al. APT 2012
**H. pylori Eradication in FD**

**Rationale:** *H. pylori* can create a cascade of events leading to gastric inflammation and immune activation.

**Outcome:** relative risk of remaining dyspeptic


**RRR:** 9%

**NNT:** 14

Those with EPS more likely to benefit

---

**H. pylori Test-and-Treat**

**Pro’s**
- Important cause of PUD
- WHO recognizes as a carcinogen
- Cost effective in decision analytic models
  - Reduced risks of EGD and associated costs

**Con’s**
- *H. pylori* is going away
  - Need to have a background rate of 10%
- *H. pylori* eradication does not help most people with dyspepsia
- Widening antibiotic resistance
**Antacids and H2RAs in FD**

- **Antacids, H2RAs**
  - Antacids (and bismuth and sucralfate) not significantly better than placebo
  - H2RA – 11 trials (2164 pts);
    - RRR 22% (7-35%)
    - NNT 7
  - Significant heterogeneity
  - Publication bias suggested

  > Moayyedi P et al. APT 2003

**RCTs of PPIs in FD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talley (Bond) 98</td>
<td>0.77 (0.69,0.87)</td>
<td>14.3</td>
</tr>
<tr>
<td>Talley (Opera) 98</td>
<td>0.99 (0.88,1.11)</td>
<td>14.4</td>
</tr>
<tr>
<td>Boling-Sternevald 02</td>
<td>0.86 (0.74,1.01)</td>
<td>12.2</td>
</tr>
<tr>
<td>Peura (M96) 04</td>
<td>0.80 (0.70,0.90)</td>
<td>13.7</td>
</tr>
<tr>
<td>Peura (M97) 04</td>
<td>0.80 (0.71,0.91)</td>
<td>14.0</td>
</tr>
<tr>
<td>Wong 02</td>
<td>1.09 (0.97,1.23)</td>
<td>14.0</td>
</tr>
<tr>
<td>Blum 00</td>
<td>0.82 (0.75,0.90)</td>
<td>15.6</td>
</tr>
<tr>
<td>Farup 99</td>
<td>0.54 (0.27,1.06)</td>
<td>1.8</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.86 (0.78,0.95)</td>
<td></td>
</tr>
</tbody>
</table>

- **NNT = 9**
- **Significant heterogeneity between trials**
- **Response better in reflux and epigastric pain subgroups (?)**
- **No diff between standard and low dose PPI**

> Moayyedi P et al. Gastro 2004

**PPI vs. H2RA**

2 trials

RR 0.93 (0.84-1.02)
Prokinetic Therapy in FD

- Consider when predominant symptoms include postprandial fullness, bloating and/or nausea
- Meta-analysis including 14 trials (1053 pts)
  - All but 1 trial involved cisapride (not available)
  - Significant heterogeneity
  - Publication bias

Moayyedi P et al. APT 2003

Prokinetic Therapy in FD

- High quality studies of metoclopramide and domperidone in FD lacking
- Two high quality tegaserod (5-HT₄ agonist) RCTs in FD
  - 2667 women only
  - Only modest benefit (mostly in those with severe symptoms)
  - No longer available
- Itopride (D2/acetylcholinesterase antagonist)/Mosapride (5-HT₄ agonist/5-HT₃ antagonist); no better than placebo in 2 large trials
  - Available only in Japan
- ABT-299 (motilin agonist); no better than placebo
- Prucalopride (highly selective 5-HT₄ agonist); data lacking in FD
  - Not available in the U.S.

Moayyedi P et al. APT 2003
Talley NJ et al. Gastro 2005
Vakil N et al. AJG 2008
Visceral Pain Modulation in FD

- **Antidepressants (Tricyclics, SSRI, SNRI)**
  - Systematic reviews show benefit in IBS and chronic pain syndromes
  - No benefit of venlaxafine or sertraline
  - Recently reported results of the FDTT suggest benefit of amitriptyline

- **Anti-epileptics**
  - Commonly used in chronic pain syndromes
  - Gabapentin, pregabalin most commonly
  - *Post hoc* analysis of RCTs in generalized anxiety and GI symptoms showed benefit of pregabalin in treating both vs. placebo
  - No data from controlled studies in FD

- **Somatostatin analogues (octreotide)**
  - Effect on visceral sensation
  - No data from controlled studies in FD

---

Functional Dyspepsia Treatment Trial (FDTT)

- **Parallel group, double blind, randomized, placebo-controlled, three-arm multi-center trial**
  - 12 week treatment period comparing amitriptyline 50 mg to escitalopram 10 mg
  - Primary endpoint: adequate symptom relief in ≥5 of the final 10 weeks

- **Rome 2 FD with normal EGD within 5 years**
  - Incomplete response to PPI
  - Excluded those with predominant reflux symptoms, regular users of NSAIDs and those taking psychotropic medication for depression or psychosis, or eating disorders

- **Mechanistic endpoints**
  - Assess gastric emptying, postprandial satiation and gastric volume change with a meal with these therapies

---

Tan VP et al. WJG 2012
Lacy BE et al. APT 2012

Talley NJ et al. Gastro 2015
FDTT Results

- 292 pts (70% dysmotility-like; 30% ulcer-like)
- **Primary endpoint:** 39 placebo (40%), 51 amitriptyline (53%), and 37 escitalopram (38%) (P = 0.05, after treatment, adjusted for baseline balancing factors including all subjects)
  - Subjects with ulcer-like FD given amitriptyline were >3-fold more likely to report adequate relief than those given placebo (odds ratio = 3.1; 95% confidence interval: 1.1-9.0).
- Neither amitriptyline nor escitalopram affected GE or meal-induced satiety
- Subjects with delayed GE were less likely to report adequate relief (odds ratio = 0.4; 95% confidence interval: 0.2-0.8).
- Both antidepressants improved overall quality of life

Talley NJ et al. Gastro 2015

CAM Therapy in FD

- Up to 50% of FD patients seek CAM therapies
- Consistent evidence of acupuncture, homeopathy and probiotics in FD is lacking
- **STW5 (Iberogast)**
  - Herbal preparation containing extracts of bitter candy tuft, matricaria flower, peppermint leaves, caraway, licorice root and lemon balm
  - Enhance gastric accommodation
  - Safe, well tolerated and effective in RCTs using Rome 1 and Rome 2 FD criteria and different outcome variables (20 drops TID)
- **Capsaicin**
  - Better than placebo in 1 small RCT

Von Armin U et al. AJG 2007
Bortolotti M et al. APT 2002
Lacy BE et al. APT 2012
Psychotropic Agents in FD

- Systematic review and meta-analysis of 13 studies (1241 pts)
  - 10 low risk of bias
  - NNT 6
- Benefit limited to TCA and anti-psychotics (levosulpiride)
- No benefit from SSRI, SNRI, tetracyclic antidepressants or 5-HT1A agonists
- AEs higher with these drugs
  - NNH 21

Ford AC et al. Gut 2015

Pilot Trial of Mirtazapine in FD

- Antidepressant with H1RA, α2 receptor antagonist and 5-HT2C/5-HT3 antagonist properties
- RDBPCT of 34 tertiary care pts with FD + weight loss >10% UBW
  - Absence of significant depression or anxiety
  - Mirtazapine 15 mg/d or placebo for 8 weeks
  - Evaluated symptoms, QoL, GI-specific anxiety, weight, GET, NDT
- Significant improvements compared to placebo:
  - Early satiety (not correlated to changes in anxiety/depression)
  - Body weight
  - NDT mean volume tolerance (Mirtazapine affects accommodation)
- No significant effects on:
  - Epigastric pain/burning
  - Gastric emptying

Tack J et al. CGH 2016
Psychological Therapies in FD

- Targets psychological and coping disturbances that frequently coexist in FD patients
  - Antidepressants (SSRI, SNRI), Psychotherapy (Cognitive behavioral therapy), Hypnotherapy, Applied relaxation
- Study quality generally good for antidepressant trials but poor for psychological therapies
- Many studies of psychological therapies claim benefit
  - Often suffer from inadequate blinding, biased patient recruitment, and problematic statistical analysis
- Usually reserved for those FD patients with severe and/or refractory symptoms
  - Not all patients are motivated for psychological interventions
  - Often difficult to find therapists with experience in this particular area

Soo S et al. Cochrane Database Syst Rev 2005

Investigational Agents in FD

- **Target visceral hypersensitivity**
  - Kappa opioid agonists
    - Fedotozine, asimadoline (development withdrawn)
  - Mu/kappa opioid agonist and delta opioid antagonist
    - Eluxadoline (Viberzi for IBS)
  - ? Neurokinin receptor antagonist
- **Target gastric accommodation**
  - Nitrates, sildenafil, sumatriptan
    - Probably not suitable for use in FD
  - 5-HT\textsubscript{1A} agonist
    - Buspirone (Buspar), tandospirone
  - Acotiamide - acetylcholinesterase inhibitor
    - Accelerates gastric emptying and enhances gastric accommodation
    - Large RCT in Japan showed benefit in FD (52% vs. 35%); mainly PDS
    - Phase 3 trials ongoing in the West
Functional Dyspepsia: The Problems

- Symptoms come and go (and change)
- No pathophysiologic findings present in all FD patients
- Findings may be present in asymptomatic pts
- Symptoms and findings don’t correlate
- No therapy universally effective
- No medication currently approved as FD therapy
- High (30-40%) placebo response rate
- Hard to predict response to therapy

Practical Management Approach to Dyspepsia

Ford and Talley. NEJM 2015
Rome IV: Treatment Approach to Dyspepsia

Take-Home Points

- Dyspepsia is common in the community
  - Most dyspepsia is due to functional dyspepsia
- Keep GERD and IBS separate from dyspepsia
- Optimal management strategy for FD is unclear
  - Initial EGD if alarm symptoms or age >55 years
- No drug FDA-approved to treat FD
- Treatment remains empiric based upon symptoms
- *H. pylori* test-and-treat remains appropriate
- Low-dose amitriptyline an option for the refractory patient