Functional Dyspepsia

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Brian E. Lacy, PhD, MD, FACG
Professor of Medicine
Geisel School of Medicine at Dartmouth
Chief, Section of Gastroenterology & Hepatology
Director, GI Motility Laboratory
Dartmouth-Hitchcock Medical Center
Lebanon, NH

Goals

• How do I make the diagnosis?
• Do I need to perform any tests?
• Will dietary interventions help?
• Which medications will help my patient?
• What alternative therapies help dyspeptic patients?
How Do I Make the Diagnosis?

• First - consider the diagnosis
  – Every upper GI symptom is not GERD
  – All abdominal pain is not IBS

• Weigh the prevalence against other disorders
  – Dyspepsia is common; MALS is not

• Review the symptoms

• Use Rome III definition

Uninvestigated Dyspepsia

Age > 55 or alarm features*

EGD

*Alarm features include unintentional weight loss, anemia, recurrent vomiting, odynophagia, family history of gastric cancer
Etiology of Investigated Dyspepsia: Organic vs. Functional

- Peptic ulcer disease
  - 5-15%
- GERD
  - 15-20%
- Malignancy
  - <1%
- Functional Dyspepsia
  - 70%
- Miscellaneous (biliary, pancreas, celiac, medications)

FD Defined: Rome III Criteria

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

- Postprandial distress syndrome (PDS): Meal-related FD
- Early satiety that prevents finishing a regular sized meal
- Epigastric pain
- Epigastric burning
- Symptoms present for the past 3 months, with onset at least 6 months before diagnosis
  Note that heartburn should be excluded.

Symptoms of Functional Dyspepsia

- Epigastric pain/discomfort – 90%
- Post-prandial fullness – 75-79%
- Bloating – 68-96%
- Nausea - 50-85%
- Early satiation – 50-82%
- Belching – 45-85%
- Vomiting – 20-31%
- Weight loss – 58%

Lacy et al, Aliment Pharmacol Ther 2012.

The pathophysiology of FD

Diagram adapted from Quigley EMM. Aliment Pharmacol Ther. 2004;20(S7):56
Symptoms and Gastric Emptying in FD Patients

• 218 consecutive FD patients (Rome II; mean age = 39; 69% women)
• Symptoms measured q 15 minutes for 4 hours after standardized meal
• 4-hr $^{14}$C-octanoic acid breath tests (20% delayed)
• Intensity of FD symptoms increased at 15 min intervals - 79% reported meal-related symptoms
• No correlation between symptoms and gastric emptying


Treating FD is difficult

• No medication is uniformly effective
• No medication is FDA approved
• Multiple pathophysologies
• Symptoms do not reflect pathophysiology
• Symptoms do not predict response to treatment
FD & Diet

- No large R, DB, PC studies to guide therapy
- Fats generally worsen symptoms
  - Delays gastric emptying
  - Worsens reflux
- Smaller more frequent meals generally help
- Response is variable
- Response may depend upon FD subtype

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

- 17 RCTs (3566 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 = 14 (95% CI, 10-28)
- Second meta-analysis of 10 RCTs in patients with FD followed up for 1 year after treatment for H. pylori did not show any benefit in resolution of dyspepsia symptoms compared with placebo.

Symptoms and Gastric Emptying: ABT-229

- FD Pts (n = 562; mean age = 46; 69% female)
- Multicenter, international study
- $^{13}$C-octanoic breath test for 4 hours
- Symptoms measured
- Placebo vs. 4 doses of ABT-229
- 52% of FD Pts had delayed emptying
- No association between any GI symptom and gastric emptying in FD Pts
- No improvement in symptoms with ABT-229


H$_2$RAs for Functional Dyspepsia

- Meta-analysis (2001)
- 22 RCTs in patients with nonulcer dyspepsia
- 14 studies, parallel group; 8 studies, crossover
- 15 of 22 studies found H$_2$RA 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

Meta-analysis of PPI trials for FD

- 7 RCTs (3725 patients)
- NNT = 14.6
- Sub-group analysis:
  - “ulcer-like” more likely to improve
  - “reflux-like” more likely to improve

Wang et al, Clin Gastroenterol Hepatol 2007; 5: 172-185

Antidepressants & FD: TCAs & SSRIs

- NIH FDTT
- Multicenter, prospective, randomized, 3 arms (placebo vs. amitriptyline vs. escitalopram)
- 12-week study
- NDI, symptoms, gastric emptying, nutrient drink test performed pre- and post-randomization
- Results: TCA provided greater relief of symptoms compared to placebo and SSRI (p < .05)
- No change in gastric emptying with active Rx

Talley et al, 2014, in press
SNRIs (Selective serotonin and Norepinephrine Reuptake Inhibitors)

- Venlafaxine (Effexor XR)
- Multicenter, R, DB, PC
- 160 Patients, 8 weeks of therapy; mean age = 52
- Symptoms, HRQOL, HADS measured
- Results: No difference between venlafaxine & placebo
- The absence of anxiety was an independent predictor of improvement in symptoms

Van Kerkhoven et al, Clin Gastroenterol Hepatol 2008; 6:746-752

Buspirone

- A non-sedative, non-benzodiazepine anxiolytic
- A 5HT\(_{(1A)}\)-agonist
- 30 and 40 mg significantly improved fundic relaxation compared to placebo in healthy volunteers (n = 10)\(^1\)
- R, DB, PC cross-over trial in FD patients\(^2\)
  - 17 patients (13 women; mean age = 38)
  - Barostat and breath test for gastric emptying
  - Sx and gastric accommodation improved
  - Gastric emptying of liquids was delayed

\(^1\)Tack et al, APT 2008; \(^2\)Tack et al Clin Gastro Hepatol, 2012
FD: Novel Treatment Options

- Duloxetine
- Acotiamide
- Tramadol
- Gabapentin
- Pregabalin
- Ghrelin agonists
- Capsaicin
- Iberogast
- Peppermint oil
- Caraway oil
- Artichoke leaf
- Hypnotherapy
- CBT
- Acupuncture

Acotiamide (Z-338)

- Multicenter, R, DB, PC, phase III trial
- 892 Rome III FD-PDS patients, 20-64 yrs
- Co-existing EPS allowed
- GERD and IBS patients excluded
- 100 mg acotiamide or placebo t.i.d. x 4 weeks
- Follow-up at 4 weeks
- 2 primary efficacy end points:
  - Overall treatment effect (OTE)
  - Elimination rate of 3 cardinal (meal related) Sx

Matsueda et al, Gut 2012, 61:821-828
Acotiamide (Z-338)

- Primary end point – OTE
  - 52.2% on acotiamide vs. 34.8% on placebo
  - (p < .001; NNT = 6)
- Elimination rate of all 3 meal related symptoms
  - 15.3% in acotiamide patients vs. 9% for placebo
  - (p < .001; NNT = 16)
- Adverse Events
  - 56% acotiamide vs. 60.4% placebo (n.s.)


Summary: FD Patient Care

- Reassure, educate, correct misconceptions
- Treat the predominant symptom
- Give adequate trials (8-12 weeks)
- Consider combination therapy
- Treat co-existing anxiety
  - Anxiety may drive symptom expression
- “Alternative” therapies are now standard
- No narcotics