

Functional Dyspepsia

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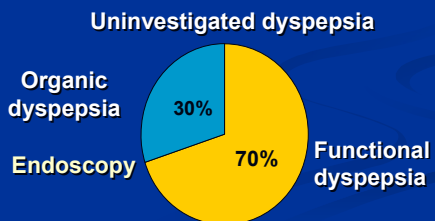
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Functional Dyspepsia: Objectives

- 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



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

Talley NJ et al. *Gastroenterology*, 1998;114: 582-595.
Tougas G et al. *Am J Gastroenterol*, 1999;94: 2845-2854.
Kennedy et al. *J Clin Gastroenterol* 2009, epub ahead of print

The Economics of Dyspepsia

- It is estimated that 10% of all healthcare expenditures in the United Kingdom go towards treating dyspepsia.
- In the United States, direct costs (diagnostic studies, emergency room 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)

Seo S et al. *Cochrane Database Sys Rev*, 2000;2:CD001960.
American Gastroenterological Association. *The Burden of Gastrointestinal Diseases*. 2001.
Weiser et al. American College of Gastroenterology Annual Meeting, Oral Presentation, 2007

Functional Dyspepsia: Unclear Natural History

- 80% of patients have symptoms 18 to 24 months after diagnosis.¹
- 74% of patients have symptoms 12 to 24 months later.²
- In contrast, some studies have shown that 30% to 50% of patients experience resolution of symptoms over the course of 12 to 24 months.^{3,4}

1. Talley NJ et al. *Am J Epidemiol.* 1992;136:165-177.
2. Jones R et al. *Br J Clin Pract.* 1992;46:95-97.
3. Bonnevie O et al. *Scand J Gastroenterol.* 1982;17:1073-1076.
4. Sloth H et al. *Scand J Gastroenterol.* 1989;24:440-444.

Functional Dyspepsia: Diagnosis



The Diagnosis of FD: 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**
 - Bothersome postprandial fullness after ordinary sized meals
 - Early satiety that prevents finishing a regular sized meal
- Epigastric pain syndrome (EPS)**
 - Epigastric pain
 - Epigastric burning

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
Note that heartburn should be excluded.

*New with Rome III criteria. Tack J et al. Gastroenterology. 2006;130:1466-1479.

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 gastrointestinal 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)

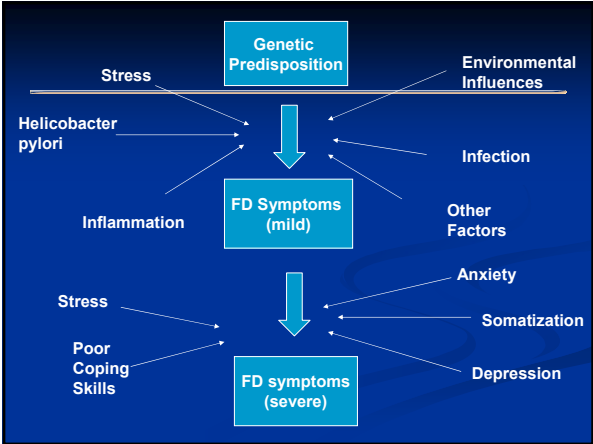
Overlap of GI motor and sensory disorders

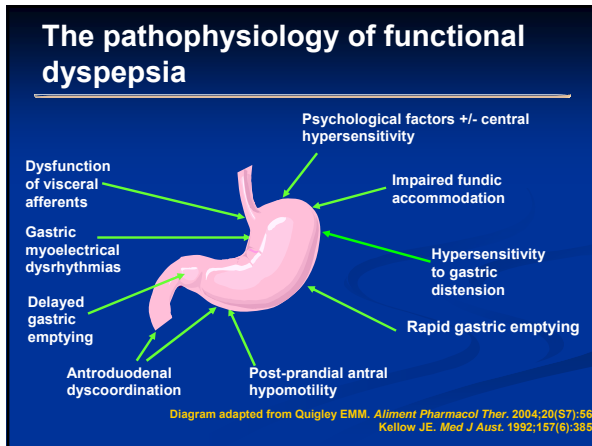
Diagnosis can shift from one disorder to another over time

Locke 3rd, et al. Neurogastroenterol Motil. 2005;17(1):29-34
Corazzari. Best Pract Res Clin Gastroenterol. 2004;18(4):613-31
Talley et al. Am J Gastroenterol. 2003;98(11):2454-9

FD: Etiology & Pathophysiology

- ### Candidate Genotypes: FD
- GNB3 (825 CC genotype)¹
 - GNB3 (TT homozygous)²
 - GNB3 (825T allele)³
 - SNPs (single nucleotide polymorphisms)⁴
 - HTR2A
 - MAGI2
 - IL-9
 - IL4R
- ¹Holtmann et al, Gastroenterology 2004, 126
²Camillieri et al, Am J Gastroenterol 2006, 101
³Van Lelyveld et al, Neurogastro & Motility 2008, 20
⁴Saito et al, ACG Annual Meeting, 2009, Poster 332, Sunday





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

70%
Functional Dyspepsia

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 healthy volunteers¹
- Small amounts of fat added to meals induces FD symptoms of bloating, fullness, and nausea^{2,3}
- A high fat meal induces more symptoms than an isocaloric high carbohydrate meal⁴
- Upper abdominal fullness and bloating was directly related to the amount of fat ingested⁵

1. Barbera et al, Eur J Gastroenterol Hepatol 1995; 7:1051-1057
2. Houghton et al, Eur J Gastroenterol Hepatol 1993; 5:109-113
3. Fattal-Bisat et al, Gut 2003; 10:1414-1418
4. Plichtiewicz et al, Am J Gastroenterol 2008; 103:2613-2623
5. Plichtiewicz et al, Clin Gastroenterol Hepatol 2009; 7:317-322

Treatment of Dyspepsia (circa 1892)

- "Therapeutic measures may be divided into those which attempt to replace in the digestive juices important elements which are lacking..."
- "In the first group come hydrochloric acid and ferments, which are so freely employed in dyspepsia."
- "Ewald recommended large doses of from 90-100 drops at intervals of 15 minutes after meals."

Osler W. The Principles and Practice of Medicine. 1892.

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 up for 1 year after treatment for *H. pylori* did not show any benefit in resolution of dyspepsia symptoms compared with placebo.

NNT, number needed to treat.

Moayyedi P et al. Am J Gastroenterol. 2003;98:2621-2626.
Laine L et al. Ann Intern Med. 2001;134:361-369.

H₂RAs 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 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

Redstone HA et al. *Aliment Pharmacol Ther.* 2001;15:1291-1299.

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

Moayyedi P et al. *Gut.* 2003;52(suppl 1):A16.

Prokinetic Agents for the Treatment of Functional Dyspepsia

Agent	Primary mode of action	Physiological effects				
		Antiemetic	Gastric emptying	Visceral sensitivity	Gastric antral motility	Gastric fundic accommodation
Metoclopramide	Dopamine antagonist 5-HT ₄ agonist	✓	↑	↓	↑	
Domperidone	Dopamine antagonist	✓	↑	↓		
Tegaserod	5-HT ₄ agonist		↑	↓	↑	↑
Levosulpiride	Dopamine antagonist 5-HT ₄ agonist	✓	↑	↓	↑	

Saad R.J. *Aliment Pharmacol Ther.* 2006;24:475-492.

Evidence for Prokinetic Therapies

- **Cisapride** – 17 studies were reviewed. Earlier apparent favorable response might have been attributed to publication bias. Recent review of 17 studies did not show any significant benefit compared with placebo.^{1,2}
- **Metoclopramide** – The most commonly used prokinetic in the treatment of FD. A recent meta-analysis failed to show any significant benefit above placebo.¹

1. Abraham NS et al. *Aliment Pharmacol Ther*. 2004;19:631-641.
2. Soo S et al. *Cochrane Database Sys Rev*. 2000;2:CD001960.

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.¹
- **Levosulpiride** – A dopamine antagonist. Not available in the United States. Recent study showed benefit compared with cisapride, though no placebo group was included.²

1. Veldhuyzen van Zanten SJO et al. *Am J Gastroenterol*. 2001;96:689-696.
2. Mearin F et al. *Clin Gastroenterol Hepatol*. 2004;2:301-308.

Emerging Therapies for Functional Dyspepsia

- Dopaminergic agents
- Serotonergic agents
- Kappa-opioid agonists
- Antidepressants
- Ghrelin
- Behavioral Therapy
- CAM
 - Capsaicin
 - Herbals

Is the glass half-empty or half-full?



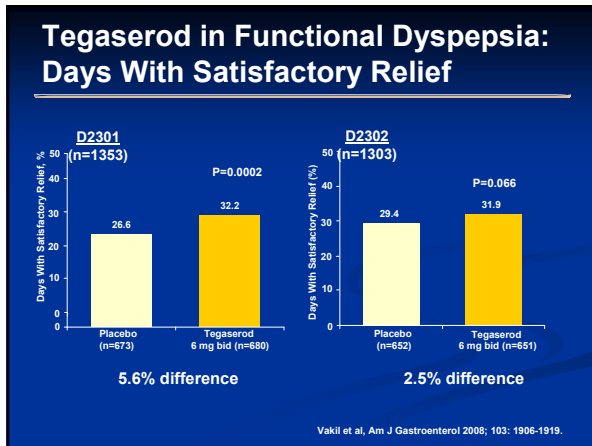
Glass Half-empty

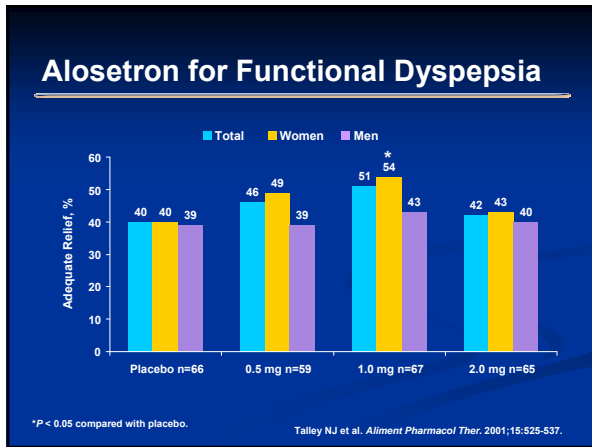
- Dopamine receptor antagonists
 - Itopride
- Serotonergic agents
 - 5-HT4 receptor agonists (Tegaserod)
 - 5-HT3 receptor antagonists (Alosetron)
- Kappa-Opioid Agonists
 - Asimadoline
- Antidepressants
 - Venlafaxine

Itopride and FD

- 2 large DB, R, PC trials (N.A. and international)
- Men and women 18-65 with FD (Rome II)
- Normal EGD; *H. pylori* (-)
- Itopride 100 mg t.i.d. vs. placebo (n = 1170)
- Global Patient Assessment (GPA) and Leeds Dyspepsia Questionnaire
- No difference in responder rates using GPA
- Leeds Dyspepsia questionnaire showed some benefit in the international group

Talley et al. Gut 2008; 57: 740-746





FD & Asimadoline

- A kappa-opioid receptor agonist
- Improves visceral pain in animal models
- Decreases pain from colonic distention
- FD Pts (Rome II) randomized to 0.5 mg or 1 mg bid x 8 weeks and compared to placebo
- No change in pain scores or daily Sx scores
- No change in MTV during nutrient drink test

Talley et al, APT 2008; 27: 1122-1131
MTV = maximum tolerated volume

FD & Venlafaxine

- An SNRI (serotonin & norepinephrine reuptake inhibitor; 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 Kerkoven et al, Clin Gastroenterol Hepatol 2008; 6:746-752

Is the glass half-empty or half-full?



FD: Glass half-full?

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

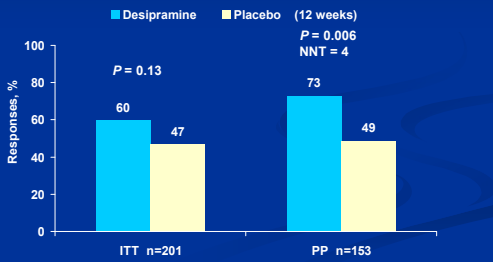
Functional Dyspepsia: TCAs

- Tricyclic antidepressants (TCAs)
 - Visceral and somatic perception are improved.¹
 - Amitriptyline improved symptoms but did not alter sensation of gastric distention.²
 - Meta-analysis in patients with FGIDs found improvement of global symptoms (OR = 4.2; NNT = 3.2) and pain³

1. Gorelick AB et al. *Am J Physiol*. 1999;275:G460-G466.
2. Mertz H. *Am J Physiol*. 1998;93:160-165.
3. Jackson JL et al. *Am J Med*. 2000;108:65-72.

Desipramine vs Placebo for Moderate to Severe FGIDs

- Better response in patients with moderate symptoms
- Dose: 50-250 mg qhs



Drossman DA et al. *Gastroenterology*. 2003;125:19-31.

Functional Dyspepsia: SSRIs/SNRIs

- Selective serotonin reuptake inhibitors (SSRIs)
 - Paroxetine did enhance gastric accommodation in healthy volunteers.¹
 - Venlafaxine was not better than placebo.
 - Mianserin or mirtazapine may be better choices.
 - NIH Functional Dyspepsia Trial in progress (TCA vs. SSRI vs. placebo)

1. Tack J et al. *Am J Physiol*. 2003;17:603-608.

FD: 5-HT1A agonists

- Tansospirone¹
 - DB, R, Placebo-controlled; Rome II criteria
 - N = 144; 4 weeks; 10 mg t.i.d. vs. placebo
 - Tansospirone improved symptoms of upper abdominal pain (p = .02) and discomfort (p = .002) more than placebo
- R-137696²
 - DB, R, Placebo-controlled; Rome II criteria
 - N = 53; 4 weeks; 2 mg tid vs. placebo
 - No difference between drug and placebo

¹Miwa et al. Am J Gastroenterol 2009, epub ahead of print
²Tack et al. Neurogastro Motility 2009, epub ahead of print

FD: Acotiamide

- Enhances ACh release – blocks M1 & M2 receptors
- Inhibits AChE activity
- Phase IIa, R, DB, placebo-controlled trial; n = 71
- Rome II FD patients; 18-65
- No effect on gastric emptying or distention
- 300 mg t.i.d. improved gastric accommodation (p=.024)
- 100 mg t.i.d. improved bloating (p = .008) and heartburn (p = .041)

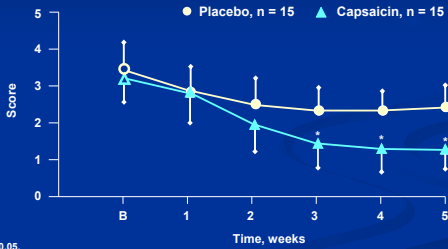
Tack et al. Neurogastro & Motil 2009; 21: 272-280.

Herbal Remedies for Functional Dyspepsia: A Systematic Review

- 17 RCTs of herbal remedies were included in the review (8 trials had a Jadad score >3).¹
- Peppermint and caraway oil were the best-studied herbal remedies.
 - 4 RCTs show 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.²

1. Thompson Coon J. *Aliment Pharmacol Ther.* 2002;16:1689-1699.
2. Gundermann KJ et al. *Adv Ther.* 2003;20:43-49.

Capsaicin for Functional Dyspepsia



*P < 0.05.
One to two capsules red pepper powder q ac.
Epigastric pain and fullness relieved.

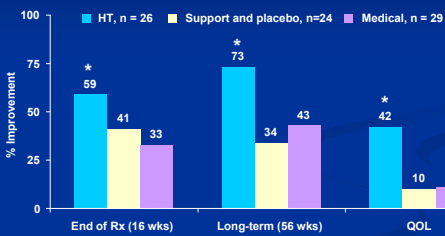
Bortolotti M et al. *Aliment Pharmacol Ther* 2002;16:1075-1082.

FD & Acupuncture

- 68 Pts with FD (Rome II criteria); randomized
- Mean age 35; 79% women
- 6-point acupuncture vs. nondefined point
- 3 sessions/week x 2 weeks
- Nepean Dyspepsia Index pre- and post-Tx
- Results: Both groups had a significant improvement in quality of life scores and symptom scores (p < .001), but no difference between the groups

Park et al. *J Alt and Complementary Medicine* 2009; 15:879-884.

Hypnotherapy for Functional Dyspepsia



*P < 0.05.
Hypnotherapy associated with less drug use and fewer visits.

Calvert EL et al. *Gastroenterology*. 2002;123:1778-1785.

Functional Dyspepsia: Potential Future Therapies

- Mianserin (tetracyclic antidepressant)
- 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 prokinetic therapy is eagerly awaited.

Functional Dyspepsia: Summary

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