Functional Dyspepsia & Nausea: Where Do We Stand in 2015?

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Functional Dyspepsia: 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
  – Functional dyspepsia is common
  – MALS is not
• Review the symptoms
• Use Rome III definition and criteria

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.
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
- Epigastric pain syndrome (EPS)

- Bothersome postprandial fullness after ordinary sized meals
- Early satiety that prevents finishing a regular sized meal
- 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.


Uninvestigated Dyspepsia

Age ≥ 55 or alarm features*

EGD

*Alarm features include unintentional weight loss, anemia, recurrent vomiting, odynophagia, or a 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, vascular)

Treating FD is difficult

- No medication is uniformly effective
- No medication is FDA approved
- Multiple pathophysiologic processes
- Symptoms do not reflect pathophysiology
- Symptoms do not predict response to treatment
The pathophysiology of FD

- Psychological factors +/- central hypersensitivity
- Impaired fundic accommodation
- Dysfunction of visceral afferents
- Gastric myoelectrical dysrhythmias
- Delayed gastric emptying
- Antroduodenal dyscoordination
- Post-prandial antral hypomotility
- Hypersensitivity to gastric distension
- Rapid gastric emptying

FD & Diet

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

Diagram adapted from Quigley EMM. Aliment Pharmacol Ther. 2004;20(S7):56
**FD Treatment: H2RAs & H. Pylori**

- **H2RAs** – histamine type 2 receptor antagonists
  - Meta-analysis of 22 RCTs showed benefit
  - Significant methodologic flaws

- **H. pylori** treatment
  - Meta-analysis of 17 RCTs (n = 3566 patients)
  - Mean response rate – placebo (29%) vs. H. pylori cure (37%)
  - Relative risk of symptoms remaining = 0.91 (95% CI, 0.86-0.95)
  - NNT = 14 (95% CI, 10-28)


**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

Antidepressants & FD

- TCAs and SSRIs used, but little data until now
- Multicenter (8), R, DB, PC trial; 12 weeks
- Rome II criteria; depression = exclusionary
- 18-75 yrs; men and women; normal EGD
- TCA (amitriptyline – 50 mg) vs. SSRI (escitalopram – 10 mg) vs. placebo
- Multiple questionnaires, labs, nutrient drink test and gastric emptying scan
- Primary endpoint: adequate relief of FD symptoms for >5 of last 10 weeks

Talley et al, Gastroenterology, 2015; 149: 340-349

Functional Dyspepsia Treatment Trial

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<th>Treatment</th>
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*Mayo Clinic sites only
Functional Dyspepsia Treatment Trial

- Mean age = 44 yrs; 75% women
- Primary endpoint of adequate relief of Sx:
  - 53% amitriptyline
  - 40% placebo
  - 38% escitalopram (p = .05)
- “ulcer-like” FD Pts 3x more likely to respond to TCA than placebo
- Pts with delayed gastric emptying were less likely to respond to either TCA or SSRI
- Neither agent affected gastric emptying
- Neither agent affected meal related satiety
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


FD: Novel Treatment Options

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

Nausea Diagnosis & Treatment: Goals

- Review key definitions
- Understand the underlying pathophysiology
- Review treatment options
**Definitions**

- **Nausea** - Derived from the Greek “nautia”
  - a vague, unpleasant or uneasy feeling in the abdomen
  - often difficult to describe
  - accompanied by the sensation that vomiting might occur
  - typically preceded by anorexia

- **Objectively, nausea is associated with:**
  - a reduction in gastric tone and gastric peristalsis
  - an increase in small bowel tone
  - tachygastria
  - an increase in plasma cortisol and beta-endorphin
  - rise in plasma vasopressin (AVP)

- **Vomiting** - From the Latin “vomere” (to discharge)
  - The forceful expulsion of gastric contents through the mouth
  - Typically preceded by anorexia and nausea
  - Autonomic symptoms are usually present (hypersalivation, tachycardia, pallor, diaphoresis, lightheadedness)

- **Retching** – absence of expulsion of gastric contents

- **Regurgitation** – effortless movement of gastric contents into the mouth and throat
N & V: A Protective Mechanism

- Robert Boyle (Irish; 1627-1691): “Tis profitable for man that his stomach should nauseate or reject things that have a loathsome taste or smell”
- Food thought to be dangerous/disgusting
- Food previously associated with N & V (conditioned taste aversion)
- Ingestion of a toxin
- Underlying gastroduodenal pathology
- Psychological factors (stress, anxiety)

CNS: Convergence on the NTS

- Vestibular system
- Area postrema
  - Chemoreceptor trigger zone
- Abdominal/vagal afferents
- Other
  - Cerebral cortex (ACC)
  - Limbic system
  - Oropharynx/gustatory
Mechanisms of Nausea

• Autonomic nervous system overactivation
• Hyperesthesia/hypersensitivity
• Adrenal gland activation
  – Splanchnic efferents
  – Catecholamine release

The Management of Nausea: Key Clinical Questions

• Is this acute or chronic?
• Are warning signs present?
• Is this related to the GI tract or to another organ system?
• Are special conditions present?
• What tests have been performed?
• What treatment options are available?
Is this Acute or Chronic?

- **Acute** - ≤ 4 weeks in duration
  - Infectious, toxins, medications, recent surgery, obstruction, inner ear disorders
- **Chronic** - > 4 weeks in duration
  - Gastroparesis
  - Dyspepsia/CUNV
  - Hepatobiliary
  - Medications
  - Functional abdominal pain
  - OIBD/Narcotic bowel syndrome
  - Psychogenic/psychological (bulimia)
  - Other (renal, cardiac, urinary, CNS, endocrine)

Are warning signs present?

- Persistent vomiting/hematemesis
- Odynophagia/dysphagia
- Unintentional weight loss
- Significant abdominal pain (out of proportion)
- Evidence of obstruction (distention)
- Associated headaches/CNS findings
- Change in mental status/vision
- Adverse events of chronic N & V
  - Dehydration, hypokalemia, metabolic alkalosis
Is nausea related to the GI tract or to another organ system?

- Musculoskeletal
- Renal
  - Nephrolithiasis, renal failure
- Urologic
  - Retention, obstruction
- Cardiac
  - CHF, arrhythmias, ischemia
- Endocrine
  - Diabetes, adrenal insufficiency
- CNS
  - Benign vs. malignant

Common GI Etiologies of Nausea

- Mucosal inflammation
  - PUD, gastritis, enteric infections, toxins, IBD, appendicitis, diverticulitis
- Functional dyspepsia
- Functional abdominal pain
- Gastroparesis
- Hepatobiliary disorders
- CIP – chronic intestinal pseudo-obstruction
- Mesenteric ischemia
- Eating disorders
- OIBD/Narcotic bowel syndrome
What treatment options are available?

- Diet
- CAM
  - Ginger, pressure band, acupuncture, acupressure
- Medications
- Behavioral therapy
- Hypnotherapy

Treatment Options:
Antiemetic Receptor Antagonists

- Histamine Receptor Antagonists
- Dopamine Receptor Antagonists
  - Butyrophenones, olanzapine, phenothiazines
- 5-HT<sub>3</sub> Receptor Antagonists
  - Granisetron, ondansetron, palonosetron
- Dopamine/5-HT<sub>3</sub> Receptor Antagonists
  - Metoclopramide, olanzapine
- NK1 Receptor Antagonists
  - Aprepitant, fosaprepitant, netupitant, rolapitant
- Others (substance P, endorphins, GABA, TRPV-1)
### Antiemetic Therapy

- Phenothiazines (promethazine, prochlorperazine)
- Antihistamines (meclizine, diphenhydramine)
- Anticholinergics (scopolamine, atropine)
- DA-2 antagonists (metoclopramide, domperidone)
- 5HT-3 antagonists (ondansetron)
- Butyrophenones (droperidol, haloperidol)
- Cannabinoids (marinol)
- Steroids (dexamethasone, prednisone)
- NK1 receptor antagonists (aprepitant)
- Others: tigan, lorazepam, olanzapine, gabapentin, opioids

### Aprepitant

- NK1 receptor antagonist (NK₁ RA)
- Inhibits binding of substance P
- May act in area postrema and NTS
- Primarily acts centrally
- 40 mg p.o. q day x 1-3 days
- FDA approved for the prevention of CINV
- Further efficacy when added to ondansetron and dexamethasone
Olanzapine

- Originally approved as an anti-psychotic
- DA-2 RA and 5-HT3 RA
- Used off-label in CINV
- 10 mg p.o. q day x 3-4 days

Chronic nausea: Conclusions

- Common
- Challenging
- All nausea is not from the GI tract
- Carefully consider the clinical utility of tests
- Treat the symptoms
- 4-6 week trials and maximize the dose
- Feel confident using combination therapies
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

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

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.)