Differentiating and Managing Dyspepsia, Gastroparesis, Rumination Syndrome and CVS

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Definitions and common misunderstandings

• Dyspepsia:
  • Defined as any upper abdominal symptom

• Limited by Rome III to:
  epigastric pain (or burning)-epigastric pain syndrome, or
  meal-related symptoms (post-prandial pain syndrome)

Overlap of Gastroparesis (GP) and Functional dyspepsia (FD)

FD- Sensory and motility disorder

ROME III:
1. One or more of following: A. Bothersome postprandial fullness, B. Early satiation C. Epigastric pain D. Epigastric burning
AND
2. No structural disease to explain symptoms (criteria fulfilled for the last 3 months with onset 6 months prior to diagnosis.

Symptoms: satiety, bloating, nausea, vomiting and weight loss in absence of mechanical obstruction + delay in gastric emptying

Longstreth et al., Gastroenterology, 2006

Functional dyspepsia induced by standard meal
Despite what patients remember, true dyspepsia symptoms all triggered by meals

Test meal 60 g white bread, egg, 300 ml water consumed within 10 min
(250 kcal: 14 g protein, 26 g carbohydrate, 10 g fat)

Traditional pathophysiology FD
Gastric pathophysiology?

- Impaired fundic accommodation
  - Functional dyspepsia with early satiety
- Delayed or rapid gastric emptying
  - Correlates very poorly with symptoms
- Hypersensitivity to gastric distention
  - Functional dyspepsia with pain


Causes of endoscopy-negative dyspepsia

- Structural and functional disease
  - Gastroesophageal reflux (often diagnosed even if no esophagitis, heartburn rare and/or PPI fails)
  - Malignancy (gastric, esophageal, liver)
  - Drugs (e.g. all NSAIDs)
  - Pancreatic disease (chronic pancreatitis); not gallstones
  - Celiac disease
  - Gastroparesis (vomiting, weight loss, very rare!)
- Functional dyspepsia (60%)
  - No structural or biochemical explanation found
New onset of dyspepsia post Salmonella gastroenteritis

Mearin et al, Gastroenterology 2005; 129: 98
Duodenal Eosinophilia (UK)

- 155 patients (mean age 55 years, 59% females) with normal duodenal biopsies at random
- Postprandial distress syndrome (PDS) mean eosinophil counts (20.2/5HPF, p<0.04) and prevalence of duodenal eosinophilia (47%, p<0.04) higher
- Duodenal eosinophilia associated with allergy (OR 5.04, 95% CI 2.12-11.95, p<0.001) but not IBS or medications

FAP: Functional abdominal pain

Homing small bowel T cells, cytokines and FD symptoms

- Cytokine release and CD4+α4β7+CCR9+ lymphocytes correlated with symptom intensity pain, cramps, nausea, vomiting
- Delayed gastric emptying correlated (r=0.78, p=0.02) with CD4+α4β7+CCR9+ lymphocytes, and IL-1β, TNF-α and IL-10 secretion
Monteleukast in FD and eosinophilia (pediatrics)

- N=40 children (6-18 yr)
- Competitive antagonist of the cys LT$_1$ receptor
- Dyspepsia & duodenal eosinophilia
- Double blind, randomized, placebo-controlled, cross-over study monteleukast 10 mg vs identical placebo once daily
- Evaluated on day 14 for symptomatic responses

Heartburn and dyspepsia – same disease spectrum?

- N=186 FD by Rome III
- Pathological acid reflux in postprandial distress syndrome 37% and epigastric pain syndrome- 29%
- 63% positive "PPI test"

Choung et al. Neurogastroenterol Motil. 2012;24:229-e106

Randomized-controlled trial of high dose PPI in FD with epigastric pain or burning

- 8 wk response rates: Esomeprazole 39% (365 of 931)
- Placebo 33% (146 of 446)
- Number needed to treat = 16

Talley et al. AP&T. 2007;26:673-82
PPI Withdrawal Induces Dyspepsia

- 58 Screened participants
- 4 Screen failures
- 54 Eligible participants
- 4 Excluded H. pylori positive
- 50 Randomly allocated
- 25 Allocated to pantoprazole
- 25 Allocated to placebo
- 2 Drop out
- 23 In analysis
- 25 In analysis

Mean symptom score

Niklasson et al. Am J Gastroenterol. 2010

H. pylori eradication efficacious

HEROES trial N= 404 patients


NNT = 17
(95% CI 11 - 33)
**Functional dyspepsia & tricyclics**

Amitryptiline and visceral hypersensitivity  
$n = 7$

![Graph showing intra-balloon volume and abdominal pain rating for Placebo and Amitryptiline.](image)


**Mirtazepine in FD**

antidepressant, anti-emetic, appetite stimulant

Diaries – early satiety (Tack et al.)

![Graph showing mean severity score (VAS) for Mirtazapine and Placebo.](image)

Early satiety
Clinical Trials Antidepressants in FD

  - venlafaxine XR (SNRI) vs. placebo, N=160
  - % symptom-free after 8 weeks venlafaxine 37% vs. placebo 39%
- Braak et al. Aliment Pharmacol Ther 2011
  - amitriptyline vs. placebo, N= 38
  - drinking capacity of liquid meal not affected
  - total symptom score on PAGI SYM (0.47 points, P=0.02) and nausea (0.86 points, P=0.004) significantly reduced by amitriptyline vs. placebo
  - amitriptyline 50 mg vs. placebo
  - cross-over trial, 4 weeks, n=7 with functional dyspepsia
  - 71% (5 of 7) reported global symptom improvement
  - 28% (2 of 7) on placebo
- Tanum and Malt. Scand J Gastro 1996
  - mianserin (5-HT-2 & 3 and alpha-2 antagonist) 120 mg vs. placebo
  - n=49 with various functional GI disorders
  - patients receiving mianserin had less pain and disability
  - FD TTT trial: Amitriptyline compared to Escitalopram versus placebo x 12 weeks (400 patients)-Nicholas Talley NIH trial

Antidepressants as neuromodulary antiemetics

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mechanism of action</th>
<th>Proposed clinical utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclics (amitriptyline, nortriptyline, desipramine)</td>
<td>Norepinephrine reuptake inhibition w/ serotonin inhibition (varied)</td>
<td>CVS, functional vomiting, ?GP/FD, N/V with diabetes</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Indirect CNS SHT1a agonism, S-HT2 antagonism</td>
<td>FD, chemo-induced nausea, hyperemesis, GP, Postop nausea</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>SHT2 Inverse agonism, M1 antagonist, SHT3 antagonism</td>
<td>Chemo-induced nausea and vomiting</td>
</tr>
</tbody>
</table>

Parakhes et al. DDS, 1998
Sawhney et al. CGH 2007
Ly et al, DDW, 2013,
Hocking et al. Supp Care Cancer 2014
New prokinetic: Acotiamide  
Inhibits cholinergic autoreceptors on nerves

- FD 100 mg acotiamide or placebo TID 4 wks in FD
- Elimination rate all 3 meal-related symptoms 15% acotiamide vs. 9% placebo (p=0.004) **NNT 16**

- Benefit over placebo maintained during 4 week post-treatment


Fundus Relaxing Drugs:  
A Therapeutic Target in FD

- Serotonin 5HT₄ agonists: cisapride
- Serotonin 1 agonists: sumatriptan (5HT₁₉), buspirone (5HT₁₈)
- STW 5

Impaired accommodation

Health
Functional dyspepsia: RCT of herbal drug STW 5

Angelicae radix (Garden angelica)
Cardui mariae fructus (Milk thistle fruits)
Carvi fructus (Caraway fruits)
Chelidonii herba
Iberis amara* (Bitter candy tuft)
Liquiritiae radix (Liquorice root)
Matricariae flos (Chamomile flowers)
Melissae folium (Balm leaves)
Menthae piperitae folium (Peppermint leaves)


Alternative therapies for FD

Interferential electric stimulation in FD

• Randomized to vacuum interferential current (IFC n=23) vs. placebo (n=21) - 12 sessions over 4 weeks

• Active therapy was superior to sham with respect to epigastric discomfort, pyrosis, bloating, early satiation and postprandial fullness during treatment (all P<0.05, ITT)

Acupuncture in FD

• N=712 randomized to acupuncture (4 types), sham or itopride
• Stomach acupuncture 71% responders vs. 35% sham

Kökülü et al. Aliment Pharmacol Ther. 2010; 31: 961-8
FD Algorithm

Gastroparesis
Symptoms and Gastric Emptying

Cannot differentiate FD from GP

* % of patients grading individual symptoms as relevant or severe (score ≥ 2)


Symptom severity assessment: The Gastroparesis Cardinal Symptom Index (GCSI)

Significant differences between gastroparesis and dyspepsia patients (n = 760) on GCSI total (p < 0.0001) and subscale scores (p < 0.03 to p < 0.0001)

Why measure gastric emptying then?

<table>
<thead>
<tr>
<th>Gastroparesis</th>
<th>Functional Dyspepsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure prokinetics</td>
<td>Combined prokinetic and antiemetic</td>
</tr>
<tr>
<td>Motilin agonists (ERY and AZI)</td>
<td>Metoclopramide</td>
</tr>
<tr>
<td>Pyloric botulinum toxin</td>
<td>Domperidone</td>
</tr>
<tr>
<td>Bethanecol</td>
<td>Most antiemetics</td>
</tr>
</tbody>
</table>

Pathophysiology of Gastroparesis

- Extrinsic denervation of vagus nerve causing delayed emptying
- Loss of nitric oxide synthase results in loss of inhibitory input to smooth muscles
  - Decreased of gastric accommodation
  - Uncordinated antral contraction
  - Pylorospasm
- Loss of heme oxygenase-1 up-regulation
  - In NOD mice leads to loss of ICC function and delayed gastric emptying
- Alteration in function of cytoprotective macrophages leading to damage to smooth muscle or ICC (such as in DM)
- Smooth muscle atrophy such as in DM decreases IGF-1 leading to ICC loss
- ICC loss leading to loss of smooth muscle contraction and dysrrhythmia

Choi et al. Gastroenterology 2008; 135: 2053-2064
### Prokinetic agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Primary mode of action</th>
<th>Physiological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Antiemetic</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Dopamine antagonist 5-HT₄ agonist</td>
<td>![ ]</td>
</tr>
<tr>
<td>Domperidone</td>
<td>Dopamine antagonist</td>
<td>![ ]</td>
</tr>
<tr>
<td>Tegaserod Prucalopride?</td>
<td>5-HT₄ agonist</td>
<td>↑</td>
</tr>
<tr>
<td>Itopride</td>
<td>Dopamine antagonist Cholinesterase inhibitor</td>
<td>![ ]</td>
</tr>
<tr>
<td>Levosulpiride</td>
<td>Dopamine antagonist 5-HT₄ agonist</td>
<td>![ ]</td>
</tr>
</tbody>
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Saad & Chey Aliment Pharmacol Ther 2006; 24: 475

### QT prolongation with GP meds

<table>
<thead>
<tr>
<th>Cardiac arrhythmias- YES</th>
<th>Cardiac arrhythmias- NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide (non-QTC)</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Domperidone (OR 3.8, 95% CI 1.5-9.7) - QTC</td>
<td>Pyloric botulinum toxin</td>
</tr>
<tr>
<td>Erythromycin (OR 2.10, 95% CI 1.08-3.75; on CYP3A inhibitors (OR 5.35, 95% CI 1.72-16.64) (QTC)</td>
<td>Gastric electrical stimulation</td>
</tr>
<tr>
<td>Clarithromycin (QTC)</td>
<td>Surgical treatments</td>
</tr>
<tr>
<td>Azithromycin (QTC)</td>
<td>Dietary changes</td>
</tr>
<tr>
<td>Ondansetron (non-QTC)</td>
<td></td>
</tr>
<tr>
<td>Promethazine (non-QTC)</td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine (non-QTC)</td>
<td></td>
</tr>
<tr>
<td>Dronabinol (non-QTC)</td>
<td></td>
</tr>
</tbody>
</table>
Transdermal Granisetron for Gastroparesis

- 5HT$_3$ receptor antagonist
- Open label study with 36 patients with GP
- Results: Symptoms (Clinical Patient Grading Scale) Improved in 18/36 (50%), worsened in 2/36
- Ratings: somewhat to moderately better
- Side effects in 25%

Simmons and Parkman, DDS 2014

Other ghrelin receptor agonists

- RM-131 (100 µg) is a synthetic ghrelin receptor agonist with longer plasma $t_{1/2}$ than TZP-102
  - Two studies show improvement in upper GI symptoms in diabetics and gastric emptying delay
  - Phase IIB studies pending

NORIG (Nortriptyline for Idiopathic Gastroparesis) Trial

- Randomized, parallel, placebo-controlled trial by NIDDK
- Gastroparesis Clinical Research Consortium (GpCRC), 7 academic centers involved
- Comparison of nortriptyline (n=65) with placebo (n=65)
- Intervention: Study dose increased every 3 weeks (10, 25, 50, 75 mg) up to 75 mg at 12 weeks
- **Primary outcome**: Decrease from baseline GCSI score of at least 50% on 2 consecutive 3-weeks during the 15 week period.
- **Drop-out rate**: 1/3 of patients due to side effects with nortriptyline
- GCSI of 21 or greater were included

**Table 4** Adjusted mean change from baseline to the end of study for total symptom score for the intent-to-treat population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline mean</th>
<th>Mean change from baseline</th>
<th>Difference from oral 10 mg Mean 95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral 10 mg</td>
<td>18</td>
<td>22.9</td>
<td>-14.1</td>
<td>-9.5 (-5.8, -13.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Nasal 10 mg</td>
<td>36</td>
<td>23.4</td>
<td>-14.4</td>
<td>-3.5 (-5.8, 0.2)</td>
<td>0.122</td>
</tr>
<tr>
<td>Nasal 20 mg</td>
<td>30</td>
<td>21.3</td>
<td>-18.0</td>
<td>-3.8 (-7.1, -0.5)</td>
<td>0.060</td>
</tr>
</tbody>
</table>

*Baseline TSS and Study Center adjusted mean change.*

**Table 5** Adjusted mean change from baseline to the end of study for total symptom score* for the per-protocol population

<table>
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<th>Treatment</th>
<th>N</th>
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<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Oral 10 mg</td>
<td>16</td>
<td>22.8</td>
<td>-13.9</td>
<td>-9.8 (-7.1, 0.5)</td>
<td>0.026</td>
</tr>
<tr>
<td>Nasal 10 mg</td>
<td>30</td>
<td>23.4</td>
<td>-17.7</td>
<td>-4.6 (-7.9, -1.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>Nasal 20 mg</td>
<td>30</td>
<td>21.3</td>
<td>-18.4</td>
<td>-3.8 (-7.1, 0.5)</td>
<td>0.060</td>
</tr>
</tbody>
</table>

*Baseline TSS and Study Center adjusted mean change.*
NORIG Trial: Changes in GCSI scores

Nortriptyline: 23% (CI: 14-35%)
Versus
Placebo 21%
(CI: 12-34%),
P value = 0.86

*No difference in Adverse events

Dropout: 29% in Nortriptyline group
Versus
9% in placebo group

Parkman et al. JAMA. 2013; 310(24); 2640-2649

Cyclic vomiting syndrome

Not necessarily meal-related
Patient is well in between episodes
Pain comes AFTER n/v
Cannabinoids and cyclic vomiting syndrome

• Described in 2004 by Allen and colleagues
• Table I Rome III Criteria for Adult Cyclic Vomiting Syndrome
• Must include all of the following:
  • 1. Stereotypical episodes of vomiting regarding onset (acute) and duration (less than one week)
  • 2. Three or more discrete episodes in the prior year
  • 3. Absence of nausea and vomiting between episodes

Supportive Criterion: History or family history of migraine headaches
  – From Rome III; the Functional Gastrointestinal Disorders.
  – Patients have compulsive bathing practices (hot showers)
  – Associations: younger age, male sex
  – CVS and cannabis use (OR 2.9, 1.2-7.2)

  • Choung et al, NGM 2012

Allen et al, Gut 2004

Treatment Options for CVS

Acute attacks
- Antiemetics
  - 5HT₃ Antagonists
- Anti-migraine meds
  - Triptans
- Benzodiazepines
  - Lorazepam
  - Clonazepam

Prophylaxis
- Tricyclics
- Anti-Epileptic drug
  - Topiramate
  - Valproate
  - Levetiracetam
  - Zonisamide
- Anti-migraine treatments
  - Beta-blockers
  - Cyproheptadine
- Mitochondrial stabilizers
  - L-Carnitine
  - Co-Enzyme A10
Antiepileptics and CVS

- TCA failure in CVS patients
- Comparison of zonisamide with levetiracetam
- Response achieved in 72% of patients
- Near resolution in 44%
- Decrease in episodes

Rumination disorder

Rumination: Voluntary but unconscious contractions of abdominal muscles forcing food return to mouth with re-chewing or swallowing

Retrograde flow of gastric contents into the mouth due to increase in gastric pressure
Psychogenic versus self-stimulating rumination
  - Psychogenic occurs in early infancy (normal development)
  - Self-Stimulating type occurs in any age, intellectual disabled patient and in healthy adults
Five times more prevalent in males

Clues in history (confused with gastroparesis, GERD and bulimia)
Weight loss seen in 83% of patients.
Regurgitation occurs in immediate postprandial stage
Diagnosis (Rome III)

Types:
- Classic rumination: Rumination without GERD
- Secondary rumination: Rumination after a reflux
- Supragastric rumination: Caused by air swallowing and then gastric straining

Characteristic finding: Gastric pressure peak >30 mmHg seen in 70% versus 0% GERD pts

Treatment: Behavioral- cognitive behavioral therapy, or biofeedback

Kessing et al. Am J Gastro 2014