Refractory GERD

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Observations about PPI use 1990-2012
A huge and expensive trend

• GERD Indications have broadened
  – In 2008, 113.4 million PPI prescriptions filled
  – 2008 sales totaled $13.9 billion

• Dosing has escalated
  – Prilosec to Nexium to Dexilant
  – 35% of US prescriptions are for (unapproved) bid dosage

• Unrealistic expectations of drug efficacy have led to
  the widespread use of term ‘PPI failure’

• Along with this massive population exposure,
  increasing recognition of potential safety issues
GERD is a condition which develops when the reflux of stomach content causes troublesome symptoms and/or complications.

### Esophageal Syndromes
- **Symptomatic Syndromes**
  - Typical reflux syndrome
  - Reflux chest pain syndrome
- **Syndromes with Esophageal Injury**
  - Reflux esophagitis
  - Reflux stricture
  - Barrett’s esophagus
  - Adenocarcinoma

### Extra-esophageal Syndromes
- **Established Association**
  - Reflux cough
  - Reflux laryngitis
  - Reflux asthma
  - Reflux dental erosions
- **Proposed Association**
  - Sinusitis
  - Pulmonary fibrosis
  - Pharyngitis
  - Recurrent otitis media

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Vakil N et al. Am J Gastroenterol 2006;101:1900

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RM #1d v2/21/10 PJK
Assessing PPI effectiveness using the Reflux Disease Questionnaire (RDQ)

- Six item self-administered questionnaire that evaluates the frequency and intensity of:
  - **Heartburn:**
    - ‘burning feeling behind the breastbone’
    - ‘pain behind the breastbone’
  - **Regurgitation:**
    - ‘acid taste in the mouth’
    - ‘unpleasant movement of material upwards from the stomach’
  - **Dyspeptic symptoms:**
    - ‘burning feeling in the center of the upper stomach’
    - ‘pain in the center of the upper stomach’

Equivalence of heartburn resolution among drugs and AZD0865 doses

Data from all treatment arms in each study were pooled to gauge the therapeutic impact of potent acid suppression on the RDQ regurgitation items compared with the heartburn item ‘burning feeling behind the breastbone’
Relative response of high severity RDQ heartburn and regurgitation items to potent acid inhibition

**Complete resolution at 4 weeks (95% CI)**

- "Substernal burning" (entry criterion)
- "Substernal pain"
- "Regurgitation-taste"
- "Regurgitation-movement"

NERD (n=1415) RE (n=1460)

High severity symptoms (≥4 days/wk of at least moderate intensity)

Regurgitation during 4th week Rx: NERD

Circle diameter proportional to # pts

Mean intensity 'Regurgitation-movement'

Mean intensity 'Regurgitation-taste'

N=83

N=132
Regurgitation during 4th week Rx: NERD

Circle diameter proportional to # pts

Mean intensity 'Regurgitation-movement'

Low

High

N=617

N=59

N=31

N=83

N=195

N=30

N=39

N=141

N=449

Mean intensity 'Regurgitation-taste'

Regurgitation during 4th week Rx: RE

Circle diameter proportional to # pts

Mean intensity 'Regurgitation-movement'

Low

High

RR#18 v1/13/12 PJK

Therapeutic gain of heartburn vs regurgitation

Systematic review: 4 weeks of PPI vs placebo treatment

- Upper limit of potential therapeutic gain

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GERD Symptoms

Attributable to GE reflux of gastric content

- Esophageal
- Heartburn
- Regurgitation
- Chest Pain
- Dysphagia
Effect of concomitant symptoms on heartburn relief

*Symptom profile at entry: RDQ heartburn items*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>NERD, n=1415</th>
<th>RE, n=1460</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substernal burning</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Substernal pain</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Proportion of patients (%)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Proportion of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substernal burning</td>
<td>Mild: 10, Moderate: 20, Severe: 30</td>
</tr>
<tr>
<td>Substernal pain</td>
<td>Mild: 10, Moderate: 20, Severe: 30</td>
</tr>
</tbody>
</table>

NERD, n=1314, 70.2% of study population
RE, n=1375, 71.4% of study population

Heartburn RDQ items during 4th week Rx: NERD

*Circle diameter proportional to # pts*

Mean intensity ‘Substernal pain’

<table>
<thead>
<tr>
<th>Mean intensity</th>
<th>N=23</th>
<th>N=60</th>
<th>N=13</th>
<th>N=288</th>
<th>N=190</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High</td>
<td></td>
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</tr>
</tbody>
</table>

Mean intensity ‘Substernal burning’
Heartburn RDQ items during 4th week Rx: RE

Circle diameter proportional to # pts

N=285
N=10
N=26
N=4
N=149
N=96

Mean intensity 'Substernal pain'

Mean intensity 'Substernal burning'

Chest pain response using PPIs in RCTs

Systematic review of trials that included GERD testing

- 7 PPI trials used pH monitoring to define GERD (+) or (-)
- 6 of these 7 used bid PPIs
- 5 trials used ≥50% improvement to define positive chest pain response; two used ≥20% improvement
- The proportion of patients reporting heartburn varied widely from zero (exclusion criterion) to essentially the entire GERD (+) population
Relief of undiagnosed chest pain (≥ 50%) with PPIs

**GERD (+) vs GERD (-) defined by pH monitoring**

![Graph showing relief of undiagnosed chest pain with PPIs.](image)

- **Upper limit of potential therapeutic gain**
- **GERD (+)**
  - Lansoprazole 30 mg daily
  - Lansoprazole 60 mg AM and 30 mg PM
  - Omeprazole 40 mg AM and 20 mg PM
  - Omeprazole 40 mg twice daily
  - Rabeprazole 20 mg twice daily
  - Global average (range)

- **GERD (-)**

**Placebo response (%)**

**Therapeutic gain with PPI (%)**

EER #11 v11/21/11 PJK

Kahrilas PJ et al. Gut 2011;60:1473

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Effect of concomitant symptoms on heartburn relief

**Treatment benefit: with vs without additional RDQ items**

- Same Esomeprazole vs AZD 0865 trial data as for regurgitation
- RDQ symptoms recorded in an e-diary twice daily
- On average, patients responded positively to 4 of the 6 RDQ items
- In both NERD and RE study, analyzed the effect of other symptoms on response of ‘burning feeling behind the breastbone’


RM #47 v5/2/11 PJK
Concomitant RDQ items affect heartburn treatment response

Treatment benefit: with vs without concomitant symptom

Concomitant (+) RDQ item

- Pain behind the breastbone
- Pain in the center of the upper stomach
- Burning feeling in the center of the upper stomach
- Unpleasant movement of material upwards from the stomach
- Acid taste in the mouth

<table>
<thead>
<tr>
<th>NERD</th>
<th>High intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagitis</td>
<td>High intensity</td>
</tr>
</tbody>
</table>

Odds ratio (95% CI) for less frequent ‘burning feeling behind the breastbone’ after 4 weeks Rx when symptom present vs symptom not present

GERD Symptoms

Attributable to GE reflux of gastric content?

- Esophageal
  - Heartburn
  - Regurgitation
  - Chest Pain
  - Dysphagia

- Extra-esophageal
  - Hoarseness
  - Cough
  - Throat clearing
  - Throat pain
  - Halitosis
  - Wheezing
  - Water brash
  - Palpitations/arrhythmias
  - Etc.
## Meta-analysis: efficacy of PPIs in cough

**Primary outcome: still coughing at the end of trial**

<table>
<thead>
<tr>
<th>Study</th>
<th>PPI n/N</th>
<th>Placebo n/N</th>
<th>Odds Ratio (95% CI)</th>
<th>Weight</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kiliarand 2000</td>
<td>7/9</td>
<td>12/12</td>
<td>8.2% 0.12 (0.01-2.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ours 1999</td>
<td>7/8</td>
<td>9/9</td>
<td>7.4% 0.26 (0.01-7.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>17</td>
<td>21</td>
<td>15.6% 0.17 (0.02-1.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ENT Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eherer 2003</td>
<td>2/5</td>
<td>4/6</td>
<td>13.5% 0.33 (0.03-3.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaezi 2006</td>
<td>79/94</td>
<td>43/48</td>
<td>70.9% 0.61 (0.21-1.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>99</td>
<td>54</td>
<td>84.4% 0.56 (0.21-1.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>116</td>
<td>75</td>
<td>100% 0.46 (0.19-1.15)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EER #23 v4-14-11 PJK
Chang AB et al. Cochrane Database, 2011

## Improvement of chronic cough with acid suppression

**GERD (+) vs GERD (-) defined by pH monitoring**

![Graph showing therapeutic gain with PPI and placebo response in GERD (+) and GERD (-) groups](image)

EER #25 v7/10/12 PJK
Kahrilas PJ et al. DDW 2012
GER-Asthma Syndrome, 770 Patients

*Esomeprazole 40 mg bid (12 weeks)*

*Three apriori patient groups*

- Nocturnal Resp Sx: yes
  - Nocturnal GERD Sx: no

- Nocturnal Resp Sx: no
  - Nocturnal GERD Sx: yes

- Nocturnal Resp Sx: yes
  - Nocturnal GERD Sx: yes

No significant difference in PEF

Morning PEF

Day -7 to +112

PEF

Eosmeprazole

Placebo

Morning PEF

Day -7 to +112

PEF

Eosmeprazole

Placebo

Morning PEF

Day -7 to +112

PEF

Eosmeprazole

Placebo

P<0.05

8.7 L/min AM Improvement

EER #6 v2-21-10 PJK


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Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma

*The American Lung Association Asthma Clinical Research Centers*

**CONCLUSIONS**

Despite a high prevalence of asymptomatic gastroesophageal reflux among patients with poorly controlled asthma, treatment with proton-pump inhibitors does not improve asthma control. Asymptomatic gastroesophageal reflux is not a likely cause of poorly controlled asthma. (ClinicalTrials.gov number, NCT00069823)

EER #27 v7/11/12 PJK

ALACRC et al. NEJM 2009;360:1487
**Lansoprazole for Children With Poorly Controlled Asthma**
A Randomized Controlled Trial

**Conclusion** In this trial of children with poorly controlled asthma without symptoms of GER who were using inhaled corticosteroids, the addition of lansoprazole, compared with placebo, improved neither symptoms nor lung function but was associated with increased adverse events.

**Trial Registration** clinicaltrials.gov Identifier: NCT00442013

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**PPI efficacy for potential manifestations of GERD**

*Estimates based on available RCT data*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Placebo</th>
<th>Therapeutic gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagitis healing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heartburn relief</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagitis NERD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regurgitation relief</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain (50% relief)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GERD (+pH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GERD (-pH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic cough (improved)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GERD (+pH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GERD (-pH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoarseness (improved)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GERD (-)</td>
<td></td>
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</tr>
</tbody>
</table>

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**RM #46 v7/10/12 PJK**

**PJ Kahrilas 2012**
Abnormal in number, composition, or volume refluxed

Montreal Definition of GERD: reflux of gastric contents causes “troublesome” symptoms

Symptom Triggers \(\approx\) Reflux events \(\times\) Acidity of gastric juice

Symptom modulators \(\approx\) Acid clearance \(\times\) Tissue sensitivity

Prolonged on basis of hiatal hernia or weak peristalsis
Montreal Definition of GERD: reflux of gastric contents causes “troublesome” symptoms

Symptom Triggers
- Reflux events
- Acid clearance

Symptom modulators
- Acidity of gastric juice
- Tissue sensitivity

Hypersensitivity - central and/or peripheral

Not a primary abnormality of GERD
PPI therapy of GERD is compensatory, not curative

**Targets of PPI therapy**

- Symptom Triggers
- Symptom modulators
- Reflux events
- Acidity of gastric juice
- Acid clearance
- Tissue sensitivity

**Causes of persistent “troublesome” symptoms**

**PPI Failures**

- Abnormal in number, composition, or volume of refluxed events
- Acid of gastric juice
- Acid clearance
- Tissue sensitivity
- Hypersensitivity - central and/or peripheral
Conceptual model of esophageal sensitivity

- Hypersensitivity
  - Increased by inflammation, permeability, sensitization

- NERD
  - Physiological → Pathological

- ‘Normal’
  - No perception → HB

- Barrett’s, stricture
  - Increased by scarring, metaplasia

Increasing Stimulus Intensity
(chemo and/or mechanoreceptors)

Pharmacological profile of TCAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>NE</th>
<th>5-HT</th>
<th>H₁</th>
<th>ACh</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>+2</td>
<td>+2</td>
<td>+4</td>
<td>+4</td>
<td>10-50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-150</td>
</tr>
<tr>
<td>Imipramine</td>
<td>+2</td>
<td>+2</td>
<td>+4</td>
<td>+2</td>
<td>10-50</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>25-150</td>
</tr>
<tr>
<td>Desipramine</td>
<td>+4</td>
<td>+2</td>
<td>+1</td>
<td>+1</td>
<td>10-50</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>25-150</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>+3</td>
<td>+2</td>
<td>+2</td>
<td>+2</td>
<td>10-50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-150</td>
</tr>
</tbody>
</table>

NE, norepinephrine; 5-HT, 5-hydroxytryptamine; H₁, histamine-H₁ receptor, Ach, acetylcholine.
Dosing TCAs for functional GI disease

- Low dose
- Initiate treatment with 10-25 mg at bedtime
- Increase in 10-25 mg increments at 4 week interval
- Watch for side effects
  - Reduce dosage
  - Find alternative drug
- May combine with SSRIs

‘Refractory GERD’ & ‘PPI Failures’ are Heterogeneous

- Persistent reflux (‘volume’ or ‘non-acid’ reflux)
  - Partial response to PPIs, heartburn usually resolves
  - Refractory chest pain and/or regurgitation
  - Potentially amenable to anti-reflux surgery
- Hypersensitivity
  - Post-inflammatory?
  - Potentially amenable to TCAs, SSRIs
- Concomitant, non-reflux symptoms
  - Dyspepsia
  - Esophageal motor disorders
  - IBS
- Questionable causality
  - ENT syndromes: laryngitis, cough, etc
  - Functional heartburn
  - Sleep apnea, sleep disturbance
  - Asthma