Unmet Needs in the Management of Gastroesophageal Reflux Disease

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Patients Report Attributes Extremely Important when Selecting Stomach Relief Medication

- Fast-acting relief (79%)
- Long lasting (67%)
- No side effects (60%)
- Effectively blocks symptoms (55%)
- Economical price (48%)
- One dose prevents breakthrough symptoms (48%)
- One dose lasts 12-24 hours (42%)
- Recommended by doctor (39%)
- Comes in a form I want (34%)
- Don’t need prescription (32%)

What are the Areas of Unmet Need in GERD?

• Advance grading of erosive esophagitis (15-30% → 20%)

Erosive Esophagitis Healing by Baseline LA Grade

Week 8

<table>
<thead>
<tr>
<th>Grade</th>
<th>Patients Healed (%)</th>
<th>Omeprazole</th>
<th>Esomeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>90.4</td>
<td>93.4*</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>81.3</td>
<td>89.4*</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>70.4</td>
<td></td>
<td>87.2*</td>
</tr>
<tr>
<td>D</td>
<td>63.8</td>
<td></td>
<td>80*</td>
</tr>
</tbody>
</table>

N=813  N=972  N=497  N=140

P<0.01 Cochran-Mantel-Haenszel.
Richter et al. Am J Gastroenterol 2002
Symptoms Persist in Some Erosive Esophagitis Patients Despite PPI Treatment

Patients With Incomplete Symptom Relief After 8 Wks of PPI Therapy

Endoscopically Confirmed Healing Rates of Refractory Reflux Esophagitis after 8 weeks of Treatment

Longitudinal changes in weekly heartburn resolution rates

20mg q.d., n=64; 10mg b.i.d., n=60; 20mg b.i.d., n=59

What are the Areas of Unmet Need in GERD?

- Advance grading of erosive esophagitis (15-30% → 20%)
- Nonerosive reflux disease (70% → 40%)

Symptom Response Rate to Standard Dose PPI Therapy in Patients with NERD versus Patients with Erosive Esophagitis

Pooled symptomatic response rate at 4 weeks (%)
NERD (N=1854) Erosive esophagitis (N=705)

Standard-dose PPI Therapy Placebo

*P<0.0001 compared with patients with NERD

Dean et al. Clin Gastroenterol Hepatol 204;2:656-664
Comparison of Response to Proton Pump Inhibitor Treatment Between NERD and Erosive Esophagitis Patients

<table>
<thead>
<tr>
<th></th>
<th>NERD</th>
<th>Erosive esophagitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lag time to sustained</td>
<td>6 days</td>
<td>4–5 days</td>
</tr>
<tr>
<td>symptomatic relief</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic response to</td>
<td>No difference</td>
<td>Increase</td>
</tr>
<tr>
<td>standard versus half dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment Comparison between Placebo and PPI Once Daily in NERD Patients (Pooled Difference in Proportion with Heartburn Resolution by Time)

Proportion of NERD Patients Responding to Treatment at 4 Weeks


N = 509
Exclude Functional Reflux Hypersensitivity and Functional Heartburn

Patient with heartburn

Endoscopy

Normal endoscopy

pH testing

Symptom index

Normal 50%

50% abnormal

37% Positive

Responsive

NERD

Functional reflux hypersensitivity

Not responsive

63%

Negative

PPI treatment

Functional heartburn
Esophageal Hypersensitivity – Very Common in NERD

Esophageal Hypersensitivity
The perception of nonpainful esophageal stimuli as being painful, and painful esophageal stimuli as more painful

86% of NERD

Pain Modulators: An Additional Treatment For NERD?

- Antidepressants: TCA’s, SSRIs, SNRIs and Trazodone
- Adenosin agonists: (theophylline)
- Serotonin agonists: (tegaserod)
- Antiepileptics: (Pregabalin)
- Peripheral neuropathy analgesics: (Gabapentin)
- Alternative and complimentary medicine

What are the Areas of Unmet Need in GERD?

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- Nonerosive reflux disease (70% → 40%)
- Postprandial heartburn (OTC market)

Postprandial Heartburn
A Therapeutic Challenge

Potassium Competitive Acid Blockers (P-CAB) - Mean steady-state intragastric pH profiles on Day 7 With Vonoprazan (TAK-438)

Jenkins R et al. Gut 2012 (Suppl.)
What are the Areas of Unmet Need in GERD?

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- **Nighttime heartburn (50% → 38%)**

Breakthrough Nighttime Symptoms on PPI Once Daily

- During sleep: 28%
- At night: 65%
- Mid day: 45%
- In the morning: 16%

N=1064

Percentage of Symptomatic GERD Patients with Relief of Nighttime Heartburn

(Esomeprazole 20 mg for 4 weeks)

Patients with relief of nighttime heartburn %

- Esomeprazole 20 mg (N=137): 34.3%
- Placebo (N=125): 10.4%

*P<0.0001 vs placebo

Johnson D et al. Aliment Pharmacol Ther 2010;32:182-190
Therapeutic options for Nighttime GERD

- Avoid eating at least 3 hours prior bedtime
- Elevate the head of the bed
- Avoid the R decubitus position in bed
- Turn off lights when enter bed and minimize disturbances to a normal sleep
- Treat with a PPI and if symptoms are primarily during nighttime - give before dinner
- Split PPI dose (am and pm before a meal)
- Add H2RA, carafate, gaviscon etc. before bedtime
- Consider non-medical treatment

The Effect of Dexlansoprazole MR on Nighttime GERD Symptoms and Sleep Disturbances

<table>
<thead>
<tr>
<th>Efficacy end point</th>
<th>Dexlansoprazole MR 30 mg, N = 152</th>
<th>Placebo, N = 153</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median percentage of nights without heartburn</td>
<td>73.1</td>
<td>35.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage of patients with relief of nocturnal heartburn during the last 7 days of treatment</td>
<td>47.5 (67/141)</td>
<td>19.6 (29/148)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage of patients with relief of GERD-related sleep disturbances during the last 7 days of treatment</td>
<td>69.7 (99/142)</td>
<td>47.9 (69/144)</td>
<td>&lt;0.001</td>
</tr>
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GERD, gastroesophageal reflux disease.

Relief= 6 of 7 nights w/ no HB, allows 1 night w/ mild HB; 6 of 7 nights w/ no GERD-related sleep disturbance
Should We Consider Combined Treatment For GERD?

**Esophageal physiology**

- **Increase**
- **Decrease**

**Sleep**

- Decrease
- Decrease

**GERD**

- Increase
- Increase

*Schey et al. Gastroenterology* 2007; 133:1787-1795
Ramelteon – Consider for Nighttime GERD

• Non-Scheduled hypnotic
• A selective MT1 and MT2 agonist
• Pharmacological structure close to omeprazole ("crude omeprazole")
• Reduce Acid secretion and improve sleep

Lokesh Jha et al JCG 2015 (in press)
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- Nighttime heartburn (50% → 38%)
- On-demand / intermittent

GERD – A Symptom Driven Disease

I have heartburn

I will take my medication

Of those taking lansoprazole or omeprazole over 30 days, how many days were they actually taken?

<table>
<thead>
<tr>
<th>On-Demand / Intermittent Treatment for GERD</th>
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<tbody>
<tr>
<td><strong>Intermittent Therapy</strong></td>
</tr>
<tr>
<td><strong>Physician driven</strong></td>
</tr>
<tr>
<td>Administration of short, pre-determined courses of therapy when symptoms recur (1 or 2 weeks duration).</td>
</tr>
<tr>
<td><strong>On-demand Therapy</strong></td>
</tr>
<tr>
<td><strong>Patient driven</strong></td>
</tr>
<tr>
<td>Consumption of medical therapy when and during periods that patients desire.</td>
</tr>
</tbody>
</table>
On-Demand Rabeprazole Therapy in Nonerosive Reflux Disease

Patient Discontinuation* (%)

Mean Weekly Antacid Consumption (n)

*Due to inadequate heartburn control.
†P < 0.00001; ‡P < 0.0011; all comparisons vs placebo.
Cost-effectiveness of Different Therapeutic Strategies

- Decision analysis
  i. Lifestyle modifications plus antacids
  ii. H2RA to endoscopy
  iii. Step-up
  iv. Step-down
  v. PPI on demand
  vi. PPI maintenance

PPI on-demand more effective and less costly

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- **Maintenance treatment** (30%)

Maintenance Treatment

Relapse Rates of Esophagitis Are High

- The majority will relapse without maintenance PPI therapy
- 15%-23% of LA grade A/B patients relapse within 6 months on maintenance PPI therapy
- 24%-41% of LA grade C/D patients relapse within 6 months on maintenance PPI therapy

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- Maintenance treatment (30%)
- On-demand / intermittent (80-90%)
- Refractory GERD (30-40%)
- Atypical manifestations of GERD (noncardiac chest pain)

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**Extraesophageal manifestations of GERD**

Comparative Trial Between Esomeprazole 40mg Twice Daily Versus Placebo In Patients With Laryngeal Manifestations Of GERD

4 months

Symptom Response

Symptom Resolution

- Esomeprazole: 14.7%
- Placebo: 16.0%

Symptom Improvement

- Esomeprazole: 42.0%
- Placebo: 46.0%

NS

Vaezi et al, Laryngoscope. 2006;116(2) 254–260
Laryngeal Manifestations Of GERD
Functional Laryngeal/Pharyngeal Disorders – Embrace Them!

- Chronic Cough
- Throat clearing
- Throat Burning
- Throat Pain
- The burning mouth syndrome

Dickman R et al. Neurogastroenterol Motil 2014;26:603-10
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- PPIs—Dependence on food for efficacy

DEXILANT Can Be Taken Without Regard to Food

Mean Intragastric pH Over Time on Day 3 While on Dexlansoprazole 90 mg Daily

Mean pH Level Over Time

Fasting
30 min after high-fat breakfast
5 min before high-fat breakfast
30 min before high-fat breakfast

Hours From Dosing

Potassium Channel Blockers

- Bind reversibly and K competitively to the ATPase (↓ plasma level → ↓ cell drug level)
- Able to inhibit the proton pump without acid activation (not meal dependent)
- Weak base that accumulates in the parietal cell canaliculus. Potency is increased as a function of the pK$_a$
- Rapid onset of effect – complete acid blockade within 30 min. of administration
- Good oral bio-availability

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- Alternative approaches to chronic PPI treatment

Alternative Therapeutic Approaches to Chronic PPI Treatment

Medical

- H2 blockers
- Antacids/ Gaviscon / sucralfate
- Prokinetics
- Baclofen
- Pain modulators

Non-Medical

- Lifestyle modifications
- Endoscopic treatment
- Anti-reflux surgery
- Linx
- Psychological interventions
- Acupuncture

Fass R. Clin Gastroenterol Hepatol 2012;10:338-345
New Area Of Unmet Need In GERD

Bariatric Surgery
Figure 1. Number of bariatric surgeries by year (provided by the ASMBS and estimated based on annual ASMBS membership).
Esophageal Stricture Post Band Ligation
Severe Erosive Esophagitis After Sleeve Gastrectomy
The End