Feeling The Burn: Assessing Long-Term Risks and Discontinuation Strategies of Proton Pump Inhibitors

Stefanie Van Boskerck, Pharm.D.
H-E-B/University of Texas Community Pharmacy PGY1
January 12th 2017
Pharmacotherapy Rounds

Objectives

Learner should be able to:

- Define and identify therapeutic strategies for managing GERD
- Review PPI drug class and approved indications
- Assess risks with long term PPI use utilizing current evidence
- Explore an as needed or tapering alternative with PPI use
- Create an alternative treatment approach based on guidelines and current evidence
Objectives

Learner should be able to:

- Define and identify therapeutic strategies for managing GERD
- Review PPI drug class and approved indications
- Assess risks with long term PPI use utilizing current evidence
- Explore an as needed or tapering alternative with PPI use
- Create an alternative treatment approach based on guidelines and current evidence

Gastroesophageal Reflux Disease (GERD)

Definition

- Gastroesophageal reflux: is a physiologic phenomenon experienced intermittently, particularly after a meal
- Gastroesophageal reflux disease (GERD): occurs when the amount of gastroesophageal reflux exceeds the normal limit, causing symptoms with or without associated eophageal mucosal injury
  - GERD with erosions OR
  - Non-Erosive Reflux Disease (NERD)
Gastroesophageal Reflux Disease (GERD) Pathophysiology

**Normal Function**

- Esophagus
  - Transports food from mouth to stomach through peristaltic contractions
- Lower esophageal sphincter (LES)
  - Relaxes, on swallowing, to allow food to enter stomach and then contracts to prevent reflux
- Normal to have some amount of reflux multiple times each day

---

Gastroesophageal Reflux Disease (GERD) Pathophysiology Continued

**Impaired Function**

- LES barrier impairment
  - Relaxation of LES
  - Low resting LES pressure
  - Increased gastric pressure
- Decreased clearance of refluxed materials from esophagus
- Decreased esophageal mucosal resistance

---

Gastroesophageal Reflux Disease (GERD) Symptoms

**Typical symptoms**
- Heartburn
- Regurgitation
- Belching
- Chest pain

**Atypical symptoms**
- Dysphagia
- Chronic cough
- Hoarseness/sore throat
- Wheeze
- Shortness of breath
- Sleep disturbances
- Earache

**Urgent Symptoms**
- Progressive dysphagia
- Odynophagia
- Bleeding
- Unexplained weight loss
- Persistent Vomiting

Gastroesophageal Reflux Disease (GERD) Diagnosis

Step 1 - Clinical History
- Presenting typical symptoms
- +/- Risk factors (obesity, pregnancy, >40 yrs old)
- Atypical or urgent? See provider, possible endoscopy

Step 2 - PPI Trial
- PPI given daily for 8 weeks
- Effective? Confirm diagnosis
- Refractory? Optimize PPI dose
- Failure? Continue to Step 3

Katz PO, Gerson LB and Vela MF. Diagnosis and management of GERD. Am J Gastroenterol 2013; 108:308–328; doi: 10.1038/ajg.2012.444
Gastroesophageal Reflux Disease (GERD) Diagnosis

**Step 1 - Clinical History**
- Presenting typical symptoms
- +/- Risk factors (obesity, pregnancy, >40 yrs old)
- Atypical or urgent? See provider, possible endoscopy

**Step 2 - PPI Trial**
- PPI given daily for 8 weeks
- Effective? Confirm diagnosis
- Refractory? Optimize PPI dose
- Failure? Continue to Step 3

**Step 3 - Upper Endoscopy**
- (+) erosion? GERD Diagnosis
- (-) erosion? pH monitoring/specialty follow-up

Gastroesophageal Reflux Disease (GERD) Treatment

<table>
<thead>
<tr>
<th>Lifestyle Intervention</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>Strong recommendation for patients (BMI &gt; 25 with recent weight gain)</td>
</tr>
<tr>
<td>Head of bed elevation</td>
<td>Head of bed elevation with foam wedge or blocks in patients with nocturnal GERD</td>
</tr>
<tr>
<td>Avoid late evening meals</td>
<td>Avoid eating meals with high fat content within 2-3 hrs of reclining</td>
</tr>
<tr>
<td>Chocolate, caffeine, spicy foods, citrus,</td>
<td>Not routinely recommended for GERD patients. Selective elimination could be</td>
</tr>
<tr>
<td>carbonated beverage cessation</td>
<td>considered, if patients note correlation with GERD symptoms and improvement with</td>
</tr>
</tbody>
</table>

Katz PO, Gerson LB and Vela MF. Diagnosis and management of GERD. Am J Gastroenterol 2013; 108:308–328; doi: 10.1038/ajg.2012.444
Gastroesophageal Reflux Disease (GERD) Treatment

GERD with no urgent symptoms

- **Lifestyle Modifications**

- **PPI**
  - Daily
  - x 8 weeks

**Katz PO, Gerson LB and Vela MF. Diagnosis and management of GERD. Am J Gastroenterol 2013; 108:308–328; doi: 10.1038/ajg.2012.444**

Gastroesophageal Reflux Disease (GERD) Treatment

GERD (+ urgent symptoms and/or erosions)

- **Lifestyle Modifications**

- **PPI**
  - Once or twice Daily
  - x up to 16 weeks
  - For moderate to severe symptoms

- **H2RA**
  - At bedtime for Nocturnal symptoms
  - not relieved w/ PPI
  - X 2 weeks

**Katz PO, Gerson LB and Vela MF. Diagnosis and management of GERD. Am J Gastroenterol 2013; 108:308–328; doi: 10.1038/ajg.2012.444**
Gastroesophageal Reflux Disease (GERD)
Treatment

- Goal: control symptoms and prevent complications of GERD

- Maintenance therapy for patients with persistent symptoms
  - Patients with moderate to severe symptoms or urgent symptoms return after 8 week trial
  - Patients with complications such as erosive esophagitis may need PPI at higher doses and for longer


Case Study

L.Y. is a 76 y/o male presenting to his community pharmacy to pick up a refill of his esomeprazole. L.Y. has a history of GERD which is currently being treated with 40 mg of esomeprazole twice a day. He reports his GERD symptoms were moderate but is well controlled by esomeprazole for the past 4 years. He tells the Pharmacist he has seen reports on T.V. that his medication could have many long-term side effects and ultimately would like to discontinue his medication.

What should the Pharmacist recommend to L.Y.?
Objectives

Learner should be able to:

- Define and identify therapeutic strategies for managing GERD
- **Review PPI drug class and approved indications**
- Assess risks with long term PPI use utilizing current evidence
- Explore an as needed or tapering alternative with PPI use
- Create an alternative treatment approach based on guidelines and current evidence

Proton Pump Inhibitors

Background

- PPIs were first released in 1989
  - omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, dexlansoprazole
- OTC use was first approved in 2003
  - omeprazole, lansoprazole, esomeprazole
- PPIs demonstrated substantial efficacy over H₂ receptor antagonists, excellent tolerability, minimal short term side effects, and minimal drug interactions
- Current use
  - Among top 3 most prescribed class of medications in U.S.
  - Commonly used longer than their recommended duration

Proton Pump Inhibitors

**Mechanism of Action**

- Parietal cells located in the gastric glands of the stomach are activated by acetylcholine, histamine, and gastrin.

- Acid production occurs when $H^+$ is released into the stomach acid at the $H^+/K^+/ATPase$ pump.

- PPIs block the terminal step in acid production by irreversibly inhibiting the function of the $H^+/K^+/ATPase$ aspect of parietal cell membranes.

---

**Overview**

- **Indications for use**
  - Healing of erosive esophagitis
  - Maintenance of erosive esophagitis
  - Treatment of GERD
  - Risk reduction for gastric ulcer associated with NSAIDs
  - *H. pylori* eradication to reduce duodenal ulcer
  - Hypersecretory conditions (ZES)
  - Short term and maintenance treatment of a duodenal ulcer
  - Stress ulcer prophylaxis

---

19


20

### Commercially Available Proton Pump Inhibitors in the United States

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosages, mg</th>
<th>IV Liquid or suspension</th>
<th>Generic</th>
<th>Over-the-counter</th>
</tr>
</thead>
<tbody>
<tr>
<td>omeprazole</td>
<td>10, 20, 40</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>esomeprazole</td>
<td>20, 40</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>lansoprazole</td>
<td>15, 30</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>dexlansoprazole</td>
<td>30, 60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pantoprazole</td>
<td>20, 40</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>rabeprazole</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Pharmacokinetic Properties of Proton Pump Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Omeprazole</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Dexlansoprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability, %</td>
<td>30–40</td>
<td>64–90</td>
<td>80–85</td>
<td>-</td>
<td>77</td>
<td>52</td>
</tr>
<tr>
<td>Time to peak plasma level (tmax, hr)</td>
<td>0.5–3.5</td>
<td>1.5</td>
<td>1.7</td>
<td>1–2, 4–5</td>
<td>2–3</td>
<td>2–5</td>
</tr>
<tr>
<td>Protein binding, %</td>
<td>95</td>
<td>97</td>
<td>97</td>
<td>96</td>
<td>98</td>
<td>96.3</td>
</tr>
<tr>
<td>Half-life, hr</td>
<td>0.5–1</td>
<td>1–1.5</td>
<td>1.6</td>
<td>1–2</td>
<td>1–1.9</td>
<td>1–2</td>
</tr>
<tr>
<td>Primary excretion</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Liver metabolism</td>
<td>CYP2C19</td>
<td>CYP2C19</td>
<td>CYP2C19</td>
<td>CYP2C19, CYP3A4</td>
<td>CYP2C19, CYP3A4</td>
<td>CYP2C19</td>
</tr>
</tbody>
</table>

Recommended Administration of Oral PPIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>omeprazole</td>
<td>before meal (time not specified)</td>
</tr>
<tr>
<td>esomeprazole</td>
<td>60 minutes before breakfast</td>
</tr>
<tr>
<td>lansoprazole</td>
<td>before breakfast (time not specified)</td>
</tr>
<tr>
<td>dglansoprazole</td>
<td>without regards to meals</td>
</tr>
<tr>
<td>pantoprazole</td>
<td>30 minutes before breakfast</td>
</tr>
<tr>
<td>rabeprazole</td>
<td>30 minutes before a meal</td>
</tr>
</tbody>
</table>


Lost in Translation?

- **Short term PPI use while in the hospital**
  - Prophylaxis of stress ulcers
  - Preventing gastrointestinal risk while receiving anticoagulation
- **Discharged on medication indefinitely**
  - A study in 2010 found roughly 70% of patients were discharged on a form of PPI therapy while being treated for acid suppressive therapy

Why are we worried about long-term treatment?

- Side effects
  - Headache, nausea, diarrhea - mild and infrequent
  - Concerns for long term use has been studied and reported for many years
- Withdrawal
  - Following discontinuation the phenomenon of RAHS has been described; leading to increased acid production in the stomach and consequently related symptoms.

Objectives

Learner should be able to:

- Define and identify therapeutic strategies for managing GERD
- Review PPI drug class and approved indications
- Assess risks with long term PPI use utilizing current evidence
- Explore an as needed or tapering alternative with PPI use
- Create an alternative treatment approach based on guidelines and current evidence
### Long-term risks that PPIs have been associated with

- *C. difficile*-associated diarrhea
- Bone fractures
- Interaction with clopidogrel
- Interaction with methotrexate
- Hypomagnesemia
- Pneumonia/upper respiratory infections
- Enteric infections
- Dementia
- SBP in patients with cirrhosis
- Mortality in patients with cirrhosis
- Acute interstitial nephritis
- Chronic kidney disease
- Mortality after PEG insertion
- Acute myocardial infarction
- Microscopic colitis
- Vitamin B12 deficiency

---

### Which are the long-term risks that PPIs have been associated with?

- *C. difficile*-associated diarrhea
- Bone fractures
- Interaction with clopidogrel
- Interaction with methotrexate
- Hypomagnesemia
- Pneumonia/upper respiratory infections
- Enteric infections
- Dementia
- SBP in patients with cirrhosis
- Mortality in patients with cirrhosis
- Acute interstitial nephritis
- Chronic kidney disease
- Mortality after PEG insertion
- Acute myocardial infarction
- Microscopic colitis
- Vitamin B12 deficiency

---


FDA-Drug Safety Communications

- Bone fractures-2011
- Hypomagnesemia-2011
- *C. difficile*-associated diarrhea (CDAD)-2012

PPIs should be prescribed at the lowest dose and shortest duration of therapy appropriate to the condition being treated.

2013 ACG Guidelines- PPI Risk

| Patients with known osteoporosis can remain on PPI therapy. Concern for hip fractures and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture. | Moderate level of evidence |

### 2013 ACG Guidelines - PPI Risk

<table>
<thead>
<tr>
<th>Patients with known <strong>osteoporosis</strong> can remain on PPI therapy. Concern for <strong>hip fractures</strong> and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture.</th>
<th>Moderate level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI therapy can be a risk factor for <em>Clostridium difficile infection</em>, and should be used with care in patients at risk.</td>
<td>Moderate level of evidence</td>
</tr>
</tbody>
</table>

---

### 2013 ACG Guidelines - PPI Risk

| Patients with known **osteoporosis** can remain on PPI therapy. Concern for **hip fractures** and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture. | Moderate level of evidence |
| PPI therapy can be a risk factor for *Clostridium difficile infection*, and should be used with care in patients at risk. | Moderate level of evidence |
| Short-term PPI usage may increase the risk of **community-acquired pneumonia**. The risk does not appear elevated in long-term users. | Moderate level of evidence |

---

### 2013 ACG Guidelines - PPI Risk

<table>
<thead>
<tr>
<th>Patients with known <strong>osteoporosis</strong> can remain on PPI therapy. Concern for <strong>hip fractures</strong> and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture.</th>
<th>Moderate level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI therapy can be a risk factor for <strong>Clostridium difficile infection</strong>, and should be used with care in patients at risk.</td>
<td>Moderate level of evidence</td>
</tr>
<tr>
<td>Short-term PPI usage may increase the risk of <strong>community-acquired pneumonia</strong>. The risk does not appear elevated in long-term users.</td>
<td>Moderate level of evidence</td>
</tr>
<tr>
<td>PPI therapy does not need to be altered in concomitant <strong>clopidogrel</strong> users as there does not appear to be an increased risk for adverse cardiovascular events.</td>
<td>High level of evidence</td>
</tr>
</tbody>
</table>

---

**Does current research change our treatment approach?**

<table>
<thead>
<tr>
<th>Patients with known <strong>osteoporosis</strong> can remain on PPI therapy. Concern for <strong>hip fractures</strong> and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture.</th>
<th>Moderate level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI therapy can be a risk factor for <strong>Clostridium difficile infection</strong>, and should be used with care in patients at risk.</td>
<td>Moderate level of evidence</td>
</tr>
<tr>
<td>Short-term PPI usage may increase the risk of <strong>community-acquired pneumonia</strong>. The risk does not appear elevated in long-term users.</td>
<td>Moderate level of evidence</td>
</tr>
<tr>
<td>PPI therapy does not need to be altered in concomitant <strong>clopidogrel</strong> users as there does not appear to be an increased risk for adverse cardiovascular events.</td>
<td>High level of evidence</td>
</tr>
</tbody>
</table>

---

### Summary of Evidence for Potential PPI-Associated Adverse Effects

<table>
<thead>
<tr>
<th>Potential Adverse Effect</th>
<th>Plausible Underlying Biological Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney disease</td>
<td>Unclear (deposit of PPIs or metabolites in the kidney stimulating an immune response)</td>
</tr>
<tr>
<td>Dementia</td>
<td>High levels of amyloid-B and deposition of amyloid-B peptides in brains of animal models</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>Reduced calcium absorption in the duodenum as a consequence of reduced hydrochloric acid in the gastric secretions</td>
</tr>
<tr>
<td><em>C. diff.</em> infection</td>
<td>Reduced gastric acidity may promote bacterial colonization in the GI tract</td>
</tr>
<tr>
<td>Micronutrient deficiencies • Vitamin B12 • Hypomagnesaemia</td>
<td>Reduced absorption</td>
</tr>
</tbody>
</table>

---

### Summary of Evidence for Potential PPI-Associated Adverse Effects

<table>
<thead>
<tr>
<th>Potential Adverse Effect</th>
<th>Types of Studies</th>
<th>Overall Quality of Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney disease</td>
<td>Observational studies</td>
<td>Very Low</td>
</tr>
<tr>
<td>Dementia</td>
<td>Observational studies</td>
<td>Very Low</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>• Randomized trials • Systematic review/meta-analysis of observational studies</td>
<td>Low or Very Low</td>
</tr>
<tr>
<td><em>C. diff.</em> infection</td>
<td>Meta-analysis of observational studies</td>
<td>Low</td>
</tr>
<tr>
<td>Micronutrient deficiencies • Vitamin B12 • Hypomagnesaemia</td>
<td>Systematic review/meta-analysis of observational studies</td>
<td>Low or Very Low</td>
</tr>
</tbody>
</table>

*GRADE Working Group

Freedberg et al. Gastroenterology. 2017;152:706-715
Case Study

L.Y. is a 76 y/o male presenting to his community pharmacy to pick up a refill of his esomeprazole. L.Y. has a history of GERD which is currently being treated with 40 mg of esomeprazole twice a day. He reports his GERD symptoms were moderate but is well controlled by esomeprazole for the past 4 years. He tells the Pharmacist he has seen reports on T.V. that his medication could have many long-term side effects and ultimately would like to discontinue his medication.

What should the Pharmacist recommend to L.Y.?

1. His PPI has some associated long-term risks but evidence is ultimately lacking.
2. Based on his past medical history he may not need maintenance therapy.
Case Study

L.Y. is a 76 y/o male presenting to his community pharmacy to pick up a refill of his esomeprazole. L.Y. has a history of GERD which is currently being treated with 40 mg of esomeprazole twice a day. He reports his GERD symptoms were moderate but is well controlled by esomeprazole for the past 4 years. He tells the Pharmacist he has seen reports on T.V. that his medication could have many long-term side effects and ultimately would like to discontinue his medication.

What is our recommendation for discontinuation?

Objectives

Learner should be able to:

- Define and identify therapeutic strategies for managing GERD
- Review PPI drug class and approved indications
- Assess risks with long term PPI use utilizing current evidence
- **Explore an as needed or tapering alternative with PPI use**
- Create an alternative treatment approach based on guidelines and current evidence
As Needed Treatment Option

Randomized, multicenter study: on-demand versus continuous maintenance treatment with esomeprazole in patients with non-erosive gastroesophageal reflux disease


<table>
<thead>
<tr>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>To compare willingness to continue treatment with esomeprazole on-demand vs. continuous maintenance therapy for symptom control in patients with non-erosive reflux disease after 6 months.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter, open-label, randomized, non-inferiority trial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients presenting to their PCP with typical symptoms of GERD for longer than 6 months</td>
</tr>
<tr>
<td>heartburn occurring $\geq 4$ days during the last 7 days before:</td>
</tr>
<tr>
<td>- endoscopy</td>
</tr>
<tr>
<td>- start of PPI treatment</td>
</tr>
<tr>
<td>- PPI therapy had been started within the last 7 days before endoscopy</td>
</tr>
</tbody>
</table>
Randomized, multicenter study: on-demand versus continuous maintenance treatment with esomeprazole in patients with non-erosive gastroesophageal reflux disease

**Exclusion Criteria**
- significant GI disorders or other disorders likely to affect the outcome of the study
- gastroduodenal ulcers within the past 2 years
- previous esophageal, gastric or duodenal surgery
- irritable bowel syndrome
- PPI use for either ≥ 10 days of the 28 days before endoscopy or ≥ 5 of the 7 days before endoscopy

**Intervention**
Endoscopy was performed at week 0: patients with esophagitis were excluded from randomization. Patients had to be heartburn-free after 4 weeks of treatment with esomeprazole 20 mg daily.
- esomeprazole 20 mg daily continuously for 6 months
- esomeprazole 20 mg on-demand for 6 months
Randomized, multicenter study: on-demand versus continuous maintenance treatment with esomeprazole in patients with non-erosive gastroesophageal reflux disease

Endpoints
- Primary outcome: discontinuation due to unsatisfactory treatment
- Secondary outcomes: reasons for treatment discontinuation
  - dissatisfaction with symptom control
  - method of administration
  - taste/size of the pill
  - adverse events, etc.

Statistical Methods
- Non-inferiority was considered with an upper limit of the one-sided 95% confidence interval was <10%
- Intention to treat analysis
- Roughly 1020 patients required to achieve 80% power

Baseline Patient Characteristics
- Baseline characteristics were similar among groups
- N=877 enrolled, 598 randomized
  - (on-demand: n=301; continuous n=297)

Results
- Discontinuation due to unsatisfactory treatment was 6.3% for on-demand and 9.8% for continuous (-3.5% [90% CI: -7.1%, 0.2%])

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage of patients (%)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIT population</td>
<td>6.3 (18)</td>
<td></td>
</tr>
<tr>
<td>Esomeprazole on-demand (n=301)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esomeprazole continuous (n=297)</td>
<td>9.8 (31)</td>
<td></td>
</tr>
<tr>
<td>Difference (on-demand minus continuous)</td>
<td>-3.5 (1.3, 0.2)</td>
<td></td>
</tr>
</tbody>
</table>

| PP population                  | 1.2 (3)                     |                          |
| Esomeprazole on-demand (n=251) |                             |                          |
| Esomeprazole continuous (n=233)| 0.8 (1)                     |                          |
| Difference (on-demand minus continuous) | 0.8 (-6, 2.1) |                          |
Randomized, multicenter study: on-demand versus continuous maintenance treatment with esomeprazole in patients with non-erosive gastroesophageal reflux disease

Author’s Conclusion
On-demand treatment with esomeprazole 20 mg was non-inferior to continuous maintenance treatment and reduced medication usage in patients with NERD who had achieved initial treatment control.

Strengths
- Randomized controlled trial
- Multinational nature of the study population
- Use of validated instruments to assess symptoms and quality of life
- Endoscopies were performed at the beginning and end of the study to assess erosion

Weaknesses
- Small sample size and length of study
- Only looked at mild symptoms and no esophagitis (NERD)
- Disagreement between investigator and patient assessment for assessing initial randomization
- No reporting of how often the on-demand patients were using their medication
- Patients were on therapy for 4 weeks instead of 8 before separating into 2 groups.

My Conclusion
Although continuous treatment had slightly better symptom control than on demand there were some potential benefits in patients with non-erosive gastroesophageal reflux disease.
# Tapering PPI Use

Feasibility of a patient-centered deprescribing process to reduce inappropriate use of proton pump inhibitors

Reeve et. al. Annals of Pharmacotherapy. 2015; 49(1) 29-38

<table>
<thead>
<tr>
<th>Objective</th>
<th>To assess the feasibility of a patient-centered deprescribing process in a population of adults with complex polypharmacy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Prospective feasibility study</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>• Current prescription for a PPI regardless of indication, dose, frequency, and duration of use</td>
</tr>
</tbody>
</table>
| Exclusion Criteria | • Documented clinically significant dementia  
|                       | • Insufficient English language skills without a translator present  
|                       | • ≤ 18 y/o |
Feasibility of a patient-centered deprescribing process to reduce inappropriate use of proton pump inhibitors

**Intervention**
- Step 1: Complete medication history
- Step 2: Identify potentially inappropriate medications
- Step 3: Determine if medication can be ceased
- Step 4: Plan and initiate withdrawal
  - Halving the dose every 2 weeks and reduction to as-needed use if the patient remained symptom free on the low dose
  - Patients could take 1 additional dose as rescue if they had symptoms.
- Step 5: Monitoring support and documentation
  - Monitoring conducted every 2 weeks at dose reduction and at 6 months post intervention.

**Recruitment**
- 72 potential patients; only 6 met criteria and consented for withdrawal
  - 3 PPI ceased
  - 3 PPI dose reduced

**Patient Characteristics**
- 70 ± 14 years old and took 14 ± 6 medications
- 93% willingness to stop medication if recommended by doctor
- Pantoprazole was most commonly prescribed
- >3 years of PPI use for most patients
  - %18 had >10 years use
Reeve et al. Annals of Pharmacotherapy. 2015; 49(1) 29-38

Table 2. Details of Participants Who Began PPI Withdrawal.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Indication</th>
<th>Duration of Use (weeks)</th>
<th>Number of Medications</th>
<th>Number of Concomitants</th>
<th>PPI Dose and Frequency of Study Initiation</th>
<th>PPI Dose and Frequency at 1 Month</th>
<th>Summary (GIS score before Withdrawal, as of 1 Month)</th>
<th>PPI Dose and Frequency at 8 Months Postwithdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>73 (Male)</td>
<td>Ulcerogenic medication (aspirin) causing ulcerogenic GERD (typical symptoms)</td>
<td>&gt;10</td>
<td>8</td>
<td>8</td>
<td>Pantoprazole 40 mg daily</td>
<td>Pantoprazole 40 mg daily</td>
<td>Nil withdrawal</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>60 (Female)</td>
<td>Ulcerogenic GERD (typical symptoms)</td>
<td>&gt;10</td>
<td>8</td>
<td>8</td>
<td>Pantoprazole 40 mg daily</td>
<td>Pantoprazole 20 mg daily</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>65 (Male)</td>
<td>Nonulcerogenic GERD (typical symptoms)</td>
<td>&gt;10</td>
<td>8</td>
<td>17</td>
<td>Esomeprazole 40 mg daily</td>
<td>Omeprazole 20 mg daily</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>49 (Female)</td>
<td>Unulcerogenic GERD (predominantly atypical symptoms)</td>
<td>&gt;10</td>
<td>8</td>
<td>19</td>
<td>Esomeprazole 40 mg daily</td>
<td>Omeprazole 20 mg daily</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>52 (Male)</td>
<td>Unulcerogenic symptoms</td>
<td>&gt;10</td>
<td>13</td>
<td>16</td>
<td>Pantoprazole 40 mg daily</td>
<td>Pantoprazole 20 mg daily</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Abbreviations: GERD, gastroesophageal reflux disease; GIS, Gastroesophageal Reflux Disease Impact Scale; PPI, proton pump inhibitor; PRN, as required.
*Includes all regular and PRN prescription and nonprescription medications.
1 Includes all acute and reactive medical conditions.
2 GIS score is average of the 3 subscales of the GIS: upper gastrointestinal symptoms, other gastrointestinal symptoms, and impact score.
Feasibility of a patient-centered deprescribing process to reduce inappropriate use of proton pump inhibitors

Author's Conclusion
This deprescribing process can safely reduce inappropriate PPI prescribing in a small proportion of people. Although the process was deemed acceptable to participations; difficulties in patient assessment and agreement for discontinuation were barriers to the feasibility.

Strengths
- Excluded patients taking PPI on an as-needed basis
- Diverse use of PPIs even with limited study size
- Patients were older and at risk for long term side effects with PPIs

Weaknesses
- Small sample size
- No endoscopies performed
- Process was time consuming; feasibility issue

My Conclusion ★
While the process may be time consuming and difficult to assess if a patient is a candidate for discontinuation; tapering method seems useful and well tolerated in practice.

Objectives

Learner should be able to:
- Define and identify therapeutic strategies for managing GERD
- Review PPI drug class and approved indications
- Assess risks with long term PPI use utilizing current evidence
- Explore an as needed or tapering alternative with PPI use
- Create an alternative treatment approach based on guidelines and current evidence
Case Study

L.Y. is a 76 y/o male presenting to his community pharmacy to pick up a refill of his esomeprazole. L.Y. has a history of GERD which is currently being treated with 40 mg of esomeprazole twice a day. He reports his GERD symptoms were moderate but is well controlled by esomeprazole for the past 4 years. He tells the Pharmacist he has seen reports on T.V. that his medication could have many long-term side effects and ultimately would like to discontinue his medication.

What is our recommendation for discontinuation?
Case Study

L.Y. is a 76 y/o male presenting to his community pharmacy to pick up a refill of his esomeprazole. L.Y. has a history of GERD which is currently being treated with 40 mg of esomeprazole twice a day. He reports his GERD symptoms were moderate but is well controlled by esomeprazole for the past 4 years. He tells the Pharmacist he has seen reports on T.V. that his medication could have many long-term side effects and ultimately would like to discontinue his medication.

Reduce dose to 20 mg twice daily for 2 weeks → 20 mg once daily for 2 weeks → then use only one once a day as needed for symptoms

Conclusions

- Further research needed with quality randomized controlled trials to assess long term side effects of PPI use
- Efficacy of PPI in GERD makes it the standard of treatment
- Current evidence of long term side effects are mainly observational and are difficult to discredit PPI use
- Limiting long-term PPI therapy based on indication
  - 14-day OTC trial
  - 8-week PPI trial
  - 16-week for severe or refractory
- Maintenance therapy only used if persistent symptoms
  - Lowest effective dose should be considered
- Promising studies for tapering and as needed PPI therapy in patients with GERD or NERD
Acknowledgments

- Evaluator
  - Hansita Patel, Pharm.D.
- Residency Program Director
  - Nathan Pope, Pharm.D., BCACP, FACA
- Preceptors
  - Amanda Kernodle, Pharm.D.
  - Lauren Clark, Pharm.D.
  - Mark Comfort, Pharm.D.
  - Gretta Leckbee, R.Ph.
  - James Weems, R.Ph.
  - Jennifer Wilbanks, R.Ph.

Questions?
Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD</td>
<td>Gastroesophageal Reflux Disease</td>
</tr>
<tr>
<td>H2RA</td>
<td>Histamine-2 Receptor Antagonist</td>
</tr>
<tr>
<td>LES</td>
<td>Lower Esophageal Sphincter</td>
</tr>
<tr>
<td>NERD</td>
<td>Non-Erosive Reflux Disease</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
</tr>
<tr>
<td>OTC</td>
<td>Over-The-Counter</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton Pump Inhibitor</td>
</tr>
<tr>
<td>PUD</td>
<td>Peptic Ulcer Disease</td>
</tr>
<tr>
<td>RAHS</td>
<td>Rebound Acid Hypersecretion</td>
</tr>
<tr>
<td>ZES</td>
<td>Zollinger-Ellison Syndrome</td>
</tr>
</tbody>
</table>

References