



## PHARMACISTS' INTERACTIVE EDUCATION CASE STUDIES

### Evidence for PPI Use in Gastroesophageal Reflux Disease, Dyspepsia, and Peptic Ulcer Disease

Unless otherwise indicated, clinical and price information in this document is taken from:

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## Case #1 – Mr. Evans

Mr. Evans is a 79-year-old man.

He has had all of his prescriptions for his hypertension and hyperlipidemia filled at your pharmacy for many years now.

He was recently started on an inhaler medication for his chronic obstructive pulmonary disease (COPD) and he just completed a two-month course of Prevacid® (lansoprazole) for his heartburn.

Today, he presents with a refill prescription from his family physician for Prevacid – 30 mg orally, daily – a one-month supply, with six refills.

He mentions to you that he is concerned about the cost of the Prevacid, and asks if you can give him something that is less expensive.

### **Question:**

**What questions might you have for Mr. Evans to help him with his concerns regarding his medications?**

You may focus on the issue of drug plan coverage and the option of switching him to the lowest cost proton pump inhibitor (PPI). However, the first important issue to explore with the patient is his need for ongoing PPI maintenance therapy.

Sample questions you could ask:

- 1) How well have your symptoms of heartburn been controlled since taking the Prevacid?
- 2) Was the Prevacid ever stopped to see if you still had symptoms that require ongoing therapy?

### **Question:**

**Assuming Mr. Evans' symptoms have been well-controlled on continuous PPI therapy, would you recommend any changes to his medication?**

## Teaching Point #1

Alternatives [PPI discontinuation, histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs), on-demand\* dosing] to long-term, regular use of standard dose PPIs for gastroesophageal reflux disease (GERD) maybe appropriate in selected patients. (Key Message #5)

- a. Approximately 20% of patients with uninvestigated GERD will remain asymptomatic off therapy for up to six months after a successful course of initial therapy (four to eight weeks) with a PPI or H<sub>2</sub>RA (Evidence Statement G1.1.2A).
- b. Continued PPI therapy is more efficacious than step-down to H<sub>2</sub>RAs for providing symptom relief (Evidence Statement G1.2.1B).
- c. Continued standard-dose PPI therapy is more efficacious than ‘on-demand’\* PPI therapy (Evidence Statement P1.2.2C).
- d. Subsequent ‘on-demand’\* PPI therapy is more efficacious than placebo or continuous standard-dose H<sub>2</sub>RAs (Evidence Statements: G1.2.2 A and B).

\*Definition for ‘on-demand’ therapy is the daily intake of a medication for a period sufficient to achieve resolution of dyspepsia or GERD symptoms. Following symptom resolution, the medication is discontinued until symptoms recur, at which point medication intake is resumed until symptoms resolve once again.

There is no clear consensus on what constitutes optimal maintenance therapy for subjects who attain symptomatic relief with PPIs. Continuation of PPIs, switching to on-demand (p.r.n.) PPI use, stepping down to H<sub>2</sub>RAs, or a trial of medication discontinuation are all reasonable options, and the treatment decision should be individualized. If the patient is asymptomatic, a discussion with his physician on the need for reassessment before deciding to commit to long-term therapy might be appropriate. You may choose to discuss the possibilities directly with the physician, or suggest that the patient bring up the issue with his physician on a follow-up visit.

**Ask the group how they would discuss this issue with the patient (optional).**

“If you have been treated for six to eight weeks, you could discuss with your doctor whether or not you need to keep taking the medication. There are other alternatives we could look at; for example, we know that although many people may need continued therapy, about one out of five people may be able to stop the medication and not have symptoms for at least six months.”

**Question:**

**Mr. Evans would like you to phone his physician to discuss the options, but before you do, he asks if there is a PPI that works just as well that is less expensive. What would you say?**

## Teaching Point #2

There are no clinically important differences among standard doses of PPIs (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, rabeprazole 20 mg, esomeprazole 20 mg) in treatment of symptomatic GERD, ENRD (endoscopy-negative reflux disease), and esophagitis. (Evidence Statement G5.1)

The COMPUS review, which included nine systematic reviews and eight random controlled trials (RCTs), determined that there are few clinically significant benefits in choosing one PPI over any other. Esomeprazole 40 mg (Nexium®) is marginally superior to standard dose PPIs in the healing of erosive esophagitis, although the absolute difference is small and insufficient to justify its routine use in place of other PPIs.

Furthermore, there are no studies which have demonstrated that any one PPI has a favourable safety profile over any other PPI. Although theoretically, rabeprazole and pantoprazole may have a lower risk of drug-drug interaction due to differences in how they are metabolized, there are no head-to-head clinical studies of drug interactions in patients with acid-related diseases.

It should be noted that the evidence is restricted to studies that measured the comparative efficacy and safety of various PPIs as initial therapy. There are no studies that have assessed the effects of switching therapy in patients whose symptoms are controlled by a given PPI.

Therefore, standard doses of PPIs may be used interchangeably when initiating therapy. Mr. Evans and his physician should be informed that there is no evidence to guide the appropriateness of switching Mr. Evans to a lower cost agent. However, in light of the comparative data available regarding the equivalence of PPIs as initial therapy, it is likely that many patients can be switched successfully. Therefore, if cost is a major concern, a trial of the lowest-cost PPI could be considered for Mr. Evans.

Based on the COMPUS pricing information shown below, Pariet® (rabeprazole sodium) and generic omeprazole are the lowest cost PPIs, so one of these medications could be chosen for Mr. Evans.

Standard-Dose PPIs	Generic Omeprazole 20 mg Daily	Pariet® Rabeprazole 20 mg Daily	Pantoloc® Pantoprazole 40 mg Daily	Prevacid® Lansoprazole 30 mg Daily	Nexium® Esomeprazole 20 mg Daily	Losec® Omeprazole 20 mg Daily
Daily Price <sup>Δ</sup>	\$1.25	\$1.30	\$1.90	\$2.00	\$2.10	\$2.20
Approximate Monthly Price <sup>†</sup>	\$43.00	\$44.40	\$61.20	\$64.00	\$66.80	\$69.60

<sup>Δ</sup> Costs may vary between regions, consult your pharmacy for exact pricing information

<sup>†</sup> Monthly price based on a 28-day supply, plus dispensing fee of \$8.00; price will vary by region

### Ask the group how they would discuss this issue with the patient (optional).

“There are other medications from the same class of medication as Prevacid® that have been shown to work just as well, but are less expensive:

- Prevacid® will cost you \$64/month (if used daily)
- If we switch you to one of the less expensive medications, such as generic omeprazole or Pariet (rabeprazole), you would pay approximately \$20 less per month and this would save you almost \$250 per year.”

## Case #2 – Susan George

Today you receive a request to refill Susan George's prescription for Pantoloc® 40 mg orally, twice daily.

On reviewing her medication profile, you note:

Allergy: Penicillin

March 1	Pantoloc 40 mg once daily (60)
Feb 3	Pantoloc 40 mg once daily (60)
Jan 5	Pantoloc 40 mg once daily (60)
Dec 4	Pantoloc 40 mg once daily (60)
Nov 6	Pantoloc 40 mg once daily (60)
Oct 4	Pantoloc 40 mg once daily (60)
Sept 28	Pantoloc 40 mg twice daily (14)
	Metronidazole 500 mg twice daily (14)
	Biaxin® 500 mg twice daily (14)

### Question:

#### What is your assessment of this medication profile?

She received an appropriate *Helicobacter pylori* (*H. pylori*) eradication regimen in September.

First-line triple therapy:

- C1-2-3" for one week, two times a day, three drugs
- Currently approved seven-day regimens
- PPI + clarithromycin (Biaxin) + amoxicillin *or* metronidazole.

She has been compliant with PPI therapy.

She has been taking PPI therapy for six months and you wonder if this is indicated.

### Question:

#### What questions might you ask Susan when she comes for her refill?

Sample questions the pharmacist could ask:

- 1) "I noticed you have been on Pantoloc for six months now; have you discussed with your doctor how long you need to be continued on this therapy?"
- 2) "Has your doctor told you why he would like to you to continue taking Pantoloc?"
- 3) "Do you still have symptoms of ulcer pain or other symptoms related to stomach upset (e.g., heartburn, acid regurgitation, excessive burping or belching, increased abdominal fullness, nausea, feeling of slow digestion) ? "

**Question:**

**Is follow-up acid suppression needed after *H. pylori* eradication therapy?**

**Teaching Point #1**

Continued treatment with a PPI after a course of *H. pylori* eradication therapy does not produce higher ulcer healing rates than eradication therapy alone in *H. pylori*-infected patients with uncomplicated duodenal ulcer. (Evidence Statement P1.2.1A)

In general, continued PPI therapy after a course of *H. pylori* eradication therapy is not indicated, except in the following circumstances: <sup>1-5</sup>

- for gastric ulcers
- for patients that remain symptomatic
- for complicated patients with large or refractory ulcers
- to ensure ulcer healing and eradication of *H. pylori*
- when patients are at high risk for recurrence/bleeding
- for a high acid secretory condition.

(While it may be difficult for the pharmacist to determine if the patient had a duodenal ulcer versus a gastric ulcer, neither is relevant as treatment for a gastric ulcer is eight weeks, and at this point the patient has received six months of therapy.)

**Question:**

**Does she require follow-up testing to confirm the *H. pylori* had been eradicated?**

Repeat testing is generally not recommended, except in circumstances in which the patient remains symptomatic.<sup>6</sup>

Serology (a blood test) cannot be used to confirm eradication as IgG antibodies against *H. pylori* remain detectable for six to twelve months after eradication of the organism. This could lead to false-positives. A Urea Breath Test or biopsy would be indicated.<sup>6</sup>

**Follow-up #1:** Susan comes into the store for her refill and you take a few minutes to discuss her Pantoloc<sup>®</sup> use. She has continued on Pantoloc<sup>®</sup> because she experienced the same ulcer symptoms the last time she tried to stop therapy. You suggest to Susan that she follow-up with her physician as repeat testing for *H. pylori* should be considered.

**Question:**

**If Susan were going to be retested for *H. pylori* due to her continuing symptoms, would her drug therapy impact *H. pylori* testing results?**

## If so, how should it be adjusted?

Antibiotics, bismuth or acid suppression intake prior to *H. pylori* testing may result in false negatives (this means the *H. pylori* test comes back “negative” but the patient is actually infected with *H. pylori*). To prevent false negative test results, Susan should discontinue her acid suppression one week prior to the *H. pylori* test and should avoid antibiotics or bismuth four weeks prior to the *H. pylori* testing.<sup>3</sup>

**Follow-up #2:** Two weeks later, you receive a phone call from Susan’s physician. He has repeated the Urea Breath Test and the results are positive. He asks your advice on what he should consider for the next step of treatment.

### Question:

**What is the next step of treatment for Susan (i.e., a patient who still has symptoms and in whom *H. Pylori* had not been successfully eradicated)?**

This would be considered an *H. pylori* eradication treatment failure. *H. pylori* eradication should be repeated and a different first-line therapy should be used (i.e., if the patient received an amoxicillin-based regimen, switch to a metronidazole-based regimen with clarithromycin and a PPI).<sup>3,7</sup>

Another option is a quadruple regimen [PPI + BMT (bismuth, metronidazole, and tetracycline) regimen],<sup>3,7</sup> with the duration of 14 days:

- Omeprazole 20 mg twice daily
- (B) Bismuth subsalicylate 30 mL four times daily
- (M) Metronidazole 500 mg four times daily
- (T) Tetracycline 500 mg four times daily.

### Question:

**Does it matter which PPI is used in either the first or second *H. pylori* eradication regimen?**

#### Teaching Point #2

All PPIs have similar efficacy in triple-therapy regimens for *H. pylori* eradication.  
(Evidence Statement P1.1.1A)

Seven systematic reviews found that, in general, there were no significant differences in *H. pylori* eradication rates among the various PPIs. Therefore, since it does not matter which PPI is chosen for either *H. pylori* eradication regimen, the lowest cost PPI should be used (refer to chart in Case #1).

## Case #3 – Frank Kelly

Frank Kelly is a 28-year-old man who loves to run marathons. He has a 20-year history of asthma for which he uses his inhaled steroid regularly.

His asthma has been well-controlled over the years. He only uses his salbutamol inhaler prior to exercising and very rarely otherwise.

He has noticed over the last few weeks that he has had problems with coughing several times per day.

He has come in for a repeat on his salbutamol inhaler, which he has not had filled for two months.

He tells you he has done some internet research and has read that heartburn can cause coughing, and that medications that reduce stomach acid can be used to treat a cough.

He is concerned that the cough is affecting his ability to train for the upcoming marathon and wonders if he should get a prescription for Losec<sup>®</sup>.

### Question:

#### What would you tell him?

The cough symptoms are most likely related to Frank Kelly's asthma. Determine if he has been exposed to asthma triggers [e.g., smoke, pollens, recent upper respiratory tract infection, use of non-steroidal anti-inflammatory drugs (NSAIDs), etc]. Find out how often he is using his Ventolin<sup>®</sup>, if he is following his peak flows, and if he is adherent to his steroid inhaler.

Acknowledge that acid reflux is sometimes thought to be a trigger for asthma symptoms. Find out if he has a burning feeling rising up from his stomach or lower chest towards his neck.

### Question:

#### Can PPIs be used for Frank's respiratory symptoms?

##### Teaching Point #1

PPIs are ineffective in the treatment of asthma, chronic cough, and laryngeal symptoms associated with GERD. (Key Message #3)

PPIs are not efficacious in improving asthma in patients with concomitant GERD. (Evidence Statement G4.1)

In the management of GERD-associated asthma, a good quality, systematic review (12 RCTs, n=432 patients, with omeprazole 20 to 80 mg or an H<sub>2</sub>RA) suggested that treatment with PPIs did not improve FEV<sub>1</sub> (functional expiratory flow volume in one second), morning expiratory flow, airway responsiveness, or frequency of inhaler use. One RCT of PPI versus placebo reported improvement in nocturnal symptom score.

## Teaching Point #2

PPIs are not efficacious in improving cough with or without GERD. (Evidence Statement G4.3)

One good quality systematic review was identified that showed that PPIs are not efficacious in improving cough associated with GERD. The evidence for this statement is limited to trials with small sample sizes that were likely underpowered, and there were diverse study populations (e.g., patients in some trials had only cough, while in others they also had other laryngeal symptoms).

PPIs are not efficacious in improving laryngeal symptoms (ie., cough, throat clearing, globus, hoarseness, sore throat) associated with reflux. ( Evidence Statement G4.2)

One good quality systematic review containing five RCTs with a total of 247 patients was identified in this area.

While PPIs may be considered for treatment of any GERD symptoms, a PPI would not be prescribed to treat Frank's cough or asthma symptoms. Current evidence would suggest they are not efficacious in improving asthma, laryngeal symptoms, and cough that may be associated with GERD.

Most important in this case is that the patient considers optimizing his asthma therapy, potentially increasing his dose of inhaled steroid, and following up, in a timely manner, with his family physician to assess his asthma control.

## Case #4 – Fran Brown

Fran Brown is a 76-year-old female who was admitted to the hospital three days ago for investigation of a possible upper gastrointestinal bleed. She has a past medical history of a gastric ulcer ten years ago.

She had a four-day history of melena and fatigue, and her hemoglobin was 100 g/L (N 120-160 g/L). She had been taking Naproxen® 500 mg three times daily for osteoarthritis of the knee. She has had hypertension for eight years.

She underwent an endoscopy, revealing a duodenal ulcer with a non-bleeding visible vessel. It was treated endoscopically with placement of a hemostatic clip.

Since the endoscopy, she had been receiving intravenous pantoprazole (80 mg bolus, then 8 mg per hour x 72 hours). She has had no evidence of recurrent bleeding, and is tolerating oral feeds. Her pantoprazole infusion was discontinued this morning.

On reviewing her chart, you note that the biopsy taken by the gastroenterologist from the gastric antrum was *H. pylori* negative.

### Question:

**Prior to the recent events, would Fran have been a candidate for NSAID ulcer prophylaxis?**

Yes; based on her age and her past history of an ulcer, Fran should have been considered for NSAID prophylaxis.

Patients should be considered for NSAID prophylaxis when:<sup>8</sup>

- There is a prior history of gastrointestinal (GI) event(s) (e.g.,ulcer, hemorrhage)
- They are over 60-years-old
- It is a high NSAID dosage (>2 x normal dose)
- They are on warfarin and NSAIDs
- They are on corticosteroid and NSAIDs.

**Follow up #1:** The medical resident noted that the medical student switched Fran from the pantoprazole infusion to pantoprazole 40 mg orally, once daily. He asks you if he should increase the dose to pantoprazole 40 mg orally, twice daily.

### Question:

**What dose of PPI should be used for ulcer healing?**

### Teaching Point #1

High- or double-dose PPIs are generally no better than standard-dose therapy in the management of NSAID-induced ulcers. (Key Message # 2)

Two RCTs with a total of 1,476 patients found that double-dose was not superior to single-dose omeprazole. Both doses were more efficacious than H<sub>2</sub>RA or misoprostol for healing of duodenal and gastric ulcers. (The studies compared omeprazole 20 mg and 40 mg with ranitidine and misoprostol. These trial results are detailed under Evidence Statements P2.1.1A – Standard dose PPI therapy for four to eight weeks produces higher healing rates of NSAIDs associated ulcers than H<sub>2</sub>RAs, when NSAIDs are continued, and P2.1.1B – Standard-dose PPI therapy for four to eight weeks produces higher healing rates of NSAID-associated ulcers than 800 µg daily misoprostol, when NSAIDs are continued.)

Therefore, Fran does not need double-dose PPI therapy. Standard dose PPI therapy is sufficient.

### Question:

**Fran is concerned about the cost of her new medication. What would you advise the medical team?**

### Teaching Point #2

Standard-dose PPI therapy for four to eight weeks produces higher healing rates of NSAID-associated ulcers than H<sub>2</sub>RAs or 800 µg daily misoprostol, when NSAIDs are continued. (Evidence Statements P2.1.1A and P2.1.1B)

Three good quality RCTs reviewed the ulcer-healing success rate of various PPIs versus misoprostol or H<sub>2</sub>RAs. Overall, the PPIs had higher ulcer-healing rates at four weeks and eight weeks for both duodenal and gastric ulcers.

### Teaching Point #3

Different PPIs produce similar healing rates of NSAID-associated ulcer. (Evidence Statement P2.1.2A)

Based on these studies, it would appear that a PPI is the better choice for healing Fran's ulcer; she should therefore stay with a PPI versus switching to an H<sub>2</sub>RA or misoprostol.

There appears to be no differences in the healing rates of ulcer disease between the different PPIs. Although there have been no direct (head-to-head) comparisons, it appears PPIs are all similarly effective for treating NSAID-induced ulcers. Therefore, a standard dose of the lowest-cost PPI should be prescribed for Fran to promote healing of an established duodenal ulcer. The dose should be continued for an eight-week course.

## Question:

**Upon completion of her PPI therapy for ulcer healing, will Fran need ongoing PPI therapy?**

If Fran's NSAID must be continued, she will need NSAID prophylaxis. If possible, the preferred approach would be to try acetaminophen for her osteoarthritis (if she has not already tried it).

## Questions:

- 1) Which agent could be used to prevent a subsequent ulcer?
- 2) What about the use of an H<sub>2</sub>RA to prevent a recurrent ulcer?
- 3) Is misoprostol effective?

### Teaching Point #4

PPIs are more effective than H<sub>2</sub>RA for secondary prevention of NSAID-associated ulcer, but are similar in efficacy compared to misoprostol. (Evidence Statement P2.2.1B and P2.2.1C)

Standard-dose PPIs are more efficacious than standard-dose H<sub>2</sub>RAs for the secondary prevention of NSAID-associated endoscopic gastric and duodenal ulcers. (Evidence Statement P2.2.1B)

In patients with a history of ulcer, standard-dose PPIs have similar efficacy to misoprostol 400 µg to 800 µg daily for the prevention of NSAID-associated endoscopic gastric and duodenal ulcers. (Evidence Statement P2.2.1C)

Fran could either continue on her PPI, or she could be changed to misoprostol. Note: 800 µg of misoprostol was associated with significantly poorer compliance and significantly greater incidence of treatment-related adverse effects.

## Question:

**Which PPI should you chose for Fran?**

### Teaching Point #5

Different PPIs reduce ulcer risk to a similar degree when given to NSAID users for ulcer prophylaxis. (Evidence Statement P2.2.4A)

The evidence for this statement consisted of one good-quality, systematic review, and one poor-quality RCT. The review found there were no apparent differences between various PPIs from studies comparing PPIs versus other ulcer prophylaxis agents, however, there were no head-to-head trials. One RCT published since the systematic review, that directly compared omeprazole and pantoprazole, also found no significant difference in ulcer risk.

As there are no apparent differences between the various PPIs, Fran should be put on the lowest cost PPI. (See pricing chart in Case #1 of this document.)

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