Key Messages, Tips and Pearls

1. There are no clinically important differences among standard doses of PPIs in the initial treatment of most gastrointestinal conditions.
2. Double dose PPI is generally no more efficacious than standard dose as initial therapy for most GI conditions (e.g. GERD, dyspepsia, NSAID ulcer treatment & prophylaxis).
3. Assess need for ongoing therapy beyond the initial course of 4-8 weeks. Some GERD patients, especially those with erosive esophagitis (EE) will require regular PPI. [Also consider lifestyle measures, e.g. stop smoking; weight loss]
4. Periodically reassess PPI therapy. Those on high / double dose PPIs may benefit from reassessing dosage; use the lowest effective dose when maintenance therapy is required.
5. Histamine 2 receptor blockers (H2RAs) are an option for some patients with mild GERD, step-down / maintenance therapy, endoscopic negative reflux disease (ENRD), functional dyspepsia and PRN for dietary indiscretion. {Some would consider esomeprazole 40mg to be a standard dose PPI as initial therapy for most GI conditions (e.g. GERD, dyspepsia, NSAID ulcer treatment & prophylaxis).}
6. Recent safety concerns have been raised regarding PPI use. Although PPIs are quite safe, patients should use only for the duration indicated and at the lowest effective dose.
7. For patients at high risk of NSAID induced ulcers, standard dose H2RAs are NOT effective. Use a standard dose PPI.

Are there any differences in efficacy between PPIs?1,2,3

- PPIs appear more similar than different. They share a similar mechanism of action, decreasing acid secreted from the “proton pump” at the parietal cell. Systematic reviews support clinical outcome equivalency for PPIs when equivalent doses are used in the treatment of GERD,2,3,4 NSAID ulcer prophylaxis/healing and H. pylori eradication.1
- There are minor variations in pharmacokinetic profiles and drug interactions; these are seldom of clinical significance. (See Acid Suppression Drug Comparison Chart.) Variation in patient response may be seen, and is unpredictable.
- Controversy in this area surrounds esomeprazole dosing. Most literature supports that a 20mg dose is equivalent to standard doses of other PPIs; however, the 40mg dose is more commonly used. Some 40mg trials in more severe EE have shown small incremental benefit in healing.5 The marginal difference is insufficient to recommend its use over other PPIs. {Some would consider esomeprazole 40mg to be a cost-effective higher-dose PPI option.}

GERD: Initial Approach Considerations

- Standard dose PPI therapy is a treatment option and more efficacious than H2RAs for initial therapy of GERD.1
- Double dose PPI is generally no more efficacious than standard dose PPI as initial therapy for GERD (including EE).1 One review (2007 Cochrane) noted that any benefit is very modest (NNT=25).2 Some suggest that patients with a higher severity of GERD may benefit from double dose although this is unclear.

When should higher PPI doses be used?

- Double dose PPI therapy may be considered if standard doses are not effective (e.g. after 2-4 weeks of therapy).2,7 Double dose PPI should be reassessed after 4-8 weeks of therapy.2
- Lack of response to standard dose PPI warrants reassessment of the diagnosis and whether patient taking the PPI appropriately.

- The best predictor of those not likely to respond to a twice daily PPI is lack of response to a daily PPI.16
- Higher dose PPI therapy is indicated in hypersecretory conditions (e.g. Zollinger-Ellison syndrome), H. pylori eradication regimens and select patients post-GI bleed (14 weeks).
- Hospital patients discharged on PPIs should be assessed for possible dosage reduction or discontinuation.

What is the role for “On Demand” PPIs in GERD?

- “On demand” use involves starting therapy after symptoms reoccur, and discontinuing when symptoms resolve.
- Patients who relapse after initial therapy will require some form of maintenance. The lowest dose and frequency required to achieve symptom control should be used.6 20% of patients with uninvestigated GERD will not require maintenance with a PPI.7
- On demand therapy or low dose PPIs may be suitable options for ENRD. It can be considered after a successful 4-8 week initial course. Of interest, patients with ENRD who respond to initial PPI therapy require on average 0.3 doses per day.10,11

What about recent safety concerns with PPIs?

- PPIs have an excellent safety profile and few side effects. {Common SE 1-8%: headache, diarrhea, rash; Rare SE: allergy, nephritis}
- Observational data has raised concern regarding the following:
  - Fracture risk (??; with higher doses & long-term use)
  - C. difficile associated diarrhea (conflicting data)
  - Pneumonia (associated with recent initiation)
  - Low vitamin B12, iron and magnesium levels (routine monitoring not recommended)
- Summary: Given uncertainties and potential risks with long term PPI use, patients should use the lowest effective dose and only for the duration indicated. "Reassess periodically!" {See Table 3 – PPI Safety Concerns – Supplementary Data}
How effective are H2RA’s relative to PPIs?

- Standard dose PPIs for up to four weeks are more efficacious than H2RAs for improvement of reflux symptoms in the initial treatment of uninvestigated GERD. A review of 5 RCTs found symptom relief at 4-8 weeks was as follows:
  - PPI: 55-75% \{NNT = 4-6 at 4-8 weeks\}
  - H2RAs: 27-58%
- PPIs have somewhat higher efficacy for those patients with uninvestigated GERD requiring maintenance therapy.\(^\text{12}\)
- Complete symptom control at 12 months:
  - Pantoprazole: \(50\text{mg qd} \sim 77\%\) \{NNT = 6; CI: 4-13; no difference in relapse\}
  - Ranitidine: \(150\text{mg bid} \sim 59\%\) \{no difference in relapse\}
- In ENRD, PPIs offer only a slight advantage over H2RAs (improvement in 53% vs 42% at standard dose; 50% vs 44% at half-dose PPI). There was no difference in quality of life.\(^\text{1,13}\)
- PPIs are more effective than H2RAs in the treatment and maintenance of patients with erosive esophagitis.\(^\text{1,14}\)

Which patients can be trialed on an H2RA?

- H2RAs may be an effective option for the following patients:
  - mild-moderate GERD, ENRD, uninvestigated GERD
  - infrequent dietary indiscretion (H2RAs may work faster than PPIs)
  - step-down therapy following PPIs in non-erosive GERD (can be successful without affecting quality of life; reduces cost)
  - functional dyspepsia (both H2RAs and PPIs marginally effective)\(^\text{9}\)

Is it reasonable to add a nighttime H2RA for a patient having nocturnal GERD symptoms?

- H2RAs are known to provide nocturnal acid suppression. One study suggests that nighttime use in addition to a daytime PPI is useful in patients with nocturnal symptoms.\(^\text{15}\) Recent guidelines suggest this is not usually recommended. They cite the lack of evidence and the potential for tachyphylaxis to develop to H2RAs after 7 days of therapy. In such cases adding a 2nd PPI dose is likely to be more effective than a nighttime H2RA.\(^\text{8}\)

PPI cost-considerations?

- Cost differences for acid suppression regimens provide an opportunity for cost savings. A cost comparison for the PPIs is shown below in Table 1.
- Two strategies to address cost and safety concerns include:
  - initiating PPI therapy at standard dose
  - reassess use/long-term use
- PPIs are a 1.2 billion dollar market in Canada\(^\text{2004}\), and 12 billion world-wide.\(^\text{2007}\) Strategies to use low cost PPIs, lowest effective dose and periodically reassess need for therapy could save > $150 million/year in Canada.\(^\text{16}\)

### Table 1: Acid Suppression Cost Considerations

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Low Cost / $ Month</th>
<th>High Cost / $ Month</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H2RA (excluding cimetidine)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine 150mg po BID</td>
<td>$27</td>
<td>Nizatidine 150mg BID</td>
</tr>
<tr>
<td>Pantoprazole 40mg bid</td>
<td>$61</td>
<td>Esomeprazole 40mg bid</td>
</tr>
<tr>
<td>Omeprazole 20mg every other day (28)</td>
<td>$24</td>
<td>Omeprazole 20mg bid (common high dose used)</td>
</tr>
<tr>
<td><strong>$2 Dose PPI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peganolizole 10mg po daily ac</td>
<td>$33</td>
<td>Lansoprazole 15mg po daily ac</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevacid 15mg po daily ac</td>
</tr>
<tr>
<td><strong>Standard Dose PPI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole generic 20mg po daily ac</td>
<td>$52</td>
<td>Esomeprazole NEXIUM 40mg po daily ac</td>
</tr>
<tr>
<td>Omeprazole generic 20mg po daily ac</td>
<td>$52</td>
<td></td>
</tr>
<tr>
<td>Omeprazole generic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofloxacin 200mg po daily ac</td>
<td>$24</td>
<td>Misoprostol CYTOTEC 400-800mcg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Common high dose used)</td>
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<tr>
<td></td>
<td></td>
<td>(Common high dose used)</td>
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<td></td>
<td></td>
<td>(common high dose used)</td>
</tr>
</tbody>
</table>

A note on the PPI Scientific Report – March 2007: In 2005 COMPSU set up a national Expert Review Panel on PPIs. This extensive report was published in March 2007 and is available online. Panel members included: Dr. Alan B.R. Thomson (Gastroenterologist), Dr. Sander V. van Zanten (Gastroenterologist), Dr. John K. Marshall (Gastroenterologist), Dr. Laura Targownik (Gastroenterologist), Dr. Anne Holbrook (Clin Pharmacol), Dr. Melissa C. Brouwers (Methodologist), Dr. Marilyn Caughlin (PhD), Mr. Ron Goeree (Health Economist), Dr. Malcolm Man-Son-Hing (Geriatrician), Ms. Pam McLean-Veyssey (Pharmacists), Dr. John A. Rideout (FP), Dr. Brenda G. Schuster (Pharmacists).

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A Tool for Dyspepsia Management

- Figure 2 displays a clinical tool for dyspepsia management.
- The tool suggests a systematic assessment approach.

Figure 2: Dyspepsia Clinical Management Tool

Table 2: Medications & Herbs associated with GERD

<table>
<thead>
<tr>
<th>Anticholinergics</th>
<th>Proton pump inhibitors</th>
<th>Histamine H2 receptor blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenothiazine</td>
<td>Ranitidine</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Clidinium</td>
<td>Esomeprazole</td>
<td>Famotidine</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Pantoprazole</td>
<td>Ranitidine</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Omeprazole</td>
<td>Ranitidine</td>
</tr>
<tr>
<td>Nicotinic Opioid</td>
<td>Esomeprazole</td>
<td>Esomeprazole</td>
</tr>
</tbody>
</table>

Table 3: PPI Safety Concerns – Supplementary Data

Fracture risk: case control studies suggest PPIs increase the risk of hip fractures.

<table>
<thead>
<tr>
<th>Year</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.29</td>
<td>1.15-1.43</td>
</tr>
<tr>
<td>2</td>
<td>1.41</td>
<td>1.28-1.56</td>
</tr>
<tr>
<td>4</td>
<td>1.50</td>
<td>1.39-1.61</td>
</tr>
</tbody>
</table>

This risk is also associated with higher doses.

- ≤ 1.75 days/dose: OR 1.40 (95% CI = 1.26-1.54)
- > 1.75 days/dose: OR 2.65 (95% CI = 1.80-3.96)

Risk of C. difficile associated diarrhea (CDAD) and other enteric infection appears to be increased in patients on PPIs.

- OR 1.96 (95% CI = 1.28-3.00)

One Canadian study did not find an association between PPIs and hospitalization with CDAD in community elderly.

Community acquired pneumonia risk may be increased with PPIs.

- One case control study found an increase in risk of OR = 1.83-2.29

Other reported adverse reactions include low vitamin B12, iron levels and hypomagnesemic hypoparathyroidism.

Health Canada is reviewing two European studies regarding increased cardiovascular events with omeprazole and esomeprazole.

Preliminary analysis is inconclusive.

References


Figure 2: Dyspepsia Clinical Management Tool

- OVER 50% ALARM?
- NSAID?
- REFLUX?
- Gastrointestinal symptoms
- Altered weight gain
- Upper GI symptoms
- Dysphagia
- Jaundice
- Family hx

Adapted from CanDys

Table 2: Medications & Herbs associated with GERD

- Anticholinergics: atropine, hyoscyamine, anticholinesterase agents
- Proton pump inhibitors: nifedipine, felodipine, amlodipine
- Estrogen, Ethanol

Further discussion is beyond the scope of this newsletter.
Five Key Decision Points in the Approach to Patients with Uninvestigated Dyspepsia (pain or discomfort in upper abdomen) 

1. Are there other possible causes for the symptoms? Consider cardiac, hepatobiliary, medication-induced, lifestyle or dietary indiscretion
2. Is the patient <50yrs, or does the patient have alarm symptoms? Alarm features and increased age identify patients at higher risk of organic causes, including cancer and ulcers.
3. Are alarm symptoms - VBAD (Vomiting, Bleeding/anemia, Abdominal mass/uninvestigated wt loss, Dysphagia) warrant prompt investigation
4. Is the patient regularly using conventional NSAIDs (including ASA)? Stop therapy if possible
5. Is the dominant symptom heartburn or acid regurgitation, or both? If yes, these are reliable indicators of GERD (gastroesophageal reflux disease)

GERD
- symptomatic response to antisecretory therapy with proton pump inhibitor (PPI) or H2 antagonist (H2RA) is generally considered to support the presumptive diagnosis of GERD.
- mild symptomatic GERD reflux < nocturnal heartburn can often be managed with lifestyle & dietary changes along with OTC antacid or H2RA

PHARMACOLOGICAL CONSIDERATIONS
- Standard dose PPI is more efficacious than H2RA; double dose PPI is generally no more efficacious than standard dose for initial therapy in erosive esophagitis
- if symptoms recur repeat original therapy
- if symptoms not resolved, switch to a PPI x 4-8 weeks
-(b) if on a PPI give bid x 4-8 weeks or consider investigation
- (c) Ensure PPI taken ~30 minutes before am meal, or pm meal if primarily nocturnal symptoms
- Tailor the dose and frequency to control symptoms. Patients should be maintained on the lowest dose of therapy that was adequate to provide effective relief.

On-Demand PPI after response to initial PPI
- patients who respond to initial PPI therapy, subsequent “on-demand” PPI is more efficacious than continuous H2RA, but less efficacious than standard dose PPI in uninvestigated GERD

PPI treatment after H. pylori eradication
- for uncomplicated duodenal ulcer, once HP has been eradicated, continued PPI use does not produce higher ulcer healing rates and is generally not indicated
- Note: PPI may be indicated for acute healing of gastric ulcer

There are no clinically important differences among standard doses of PPIs in patients with response in dose of symptomatic GERD, ENRD and esophagitis. Patient variation in response may be seen.

STANDARD DOSES OF PPIs
- Standard dose: Omeprazole, Rabeprazole & Esomeprazole 20mg od; Lansoprazole 30mg od; Pantoprazole 40mg od.

PPIs are not efficacious in asthma associated with GERD, in improving laryngeal symptoms associated with reflux or improving chronic cough with or without GERD

COXIBs: Selective cyclooxygenase 2 inhibitors
- Drug interactions
- DU:duodenal ulcer
- H2RA: H2-receptor antagonist.
- NSAIDs: nonsteroidal anti-inflammatories
- OTC: Over the counter
- GI: gastrointestinal
- GU: genitourinary
- OTC = drug interactions

PUD & H.pylori (Non-NSAID PUD)
- 90% of DU & 70% of GU may be H.pylori positive
- the standard of care for all patients with GU/DU is H.pylori testing, treating if positive (~30% of Canadians are infected)
- smoking cessation improves ulcer healing rates and reduces ulcers not related to H.pylori infection
- diagnostic testing for H.pylori should only be performed in pts suspected of having H.pylori-related conditions such as PUD if and treatment is initiated. (test and treat strategy)
- should be used for routine diagnosis, unless endoscopy is indicated for another reason
- excellent sensitivity, specificity and ease of use
- to prevent false –ve results, patients should stop for: antibiotics 1 week, bismuth 2 weeks, PPIs 3 days & H2RA
- (pm use of antacids can be used for sx while awaiting tests)
- appropriate if no access to UBT or endoscopy, higher rate of false positives results (~20%)
- Repeat H.pylori testing after H.pylori eradication
- confirmation of H.pylori eradication is not required unless symptoms persist, pt with bleeding or perforated ulcers, MALT lymphoma or gastric cancer
- serology cannot be used to determine cure from infections (IgG antibodies still detectable 6-12 months after eradication)

H.pylori Regimens
- see H.pylori Chart; all PPIs equally effective
- 1-2-3 = drug interactions
- single and two drug regimens not recommended
- 7 & 10 regimens equally effective, but 14 day regimens more efficacious than 7 day regimens
- consider the following when selecting regimen: allergy history, recent antibiotic, metabolic status (no diabetes), etOH use (avoid metronidazole), potential compliance issues (1-2-3 regimens, Hp-PAC), Dls

PUD & NSAIDs - Prevention
- NSAIDs are responsible for the majority of HP negative PUD
- routine concomitant antilucre prophylaxis is not warranted for all pts taking NSAIDs; assess patient risk
- Prevention of NSAID Ulcers in High Risk Patients
- High Risk: especially if of HC’s UGIB. See note at bottom. Those with several risk factors are at highest risk for NSAID-induced GI toxicity (up to 9% at 6 months)
- avoid NSAID if possible (use alternatives e.g. acetaminophen)
- if NSAID must be used, use lowest dose & shortest duration

GI Ulcer Prophylaxis
- standard dose PPI (all PPIs, similar efficacy)
- misoprostol 200ug tid-qid $38-49
- not if symptoms respond to 4-8 weeks of therapy
- stop therapy, if symptoms not resolved, pt with bleeding or perforated ulcers, MALT lymphoma or gastric cancer
- HP Eradication and NSAID Use
- Antibiotics 4 weeks, bismuth 2 weeks, PPIs 3 days & H2RA
- NSAID therapy has been proposed, but is not routinely recommended, for: HP Eradication and NSAID Use
- should only be performed in patients who respond to initial PPI therapy, subsequent “on-demand” PPI is more efficacious than continuous H2RA, but less efficacious than 7 day regimens (American ACG recommends 10-14 days)
- COXIB risks {e.g. cardiac, renal, gastric} are dose dependent
- COXIBs: The GI sparing effect of COXIBs is compromised when used concurrently with low dose ASA, therefore the GI advantage of a COXIB especially at high-dose is lost. When a COXIB is used with warfarin concurrently, the risk is similar to NSAIDs.
- COXIB risks {e.g. cardiac, renal, gastric} are dose dependent
- COXIB vs {NSAID + PPI} appear to have similar efficacy in prevention and recurrence of ulcer/bleeding in patients with previous NSAID associated UGIB
- TREATMENT OF NSAID INDUCED ULCER
- Discontinue NSAID, H.pylori test & treat if positive, treat like a non-NSAID ulcer {e.g. PPI or H2RA (x4wk in DU); (x8wk in GU)}
- Healing rates: standard dose PPI x4-Weeks is more efficacious than H2RA or misoprostol

IF NSAID MUST BE CONTINUED
- PPI more effective than H2RA, but similar efficacy to misoprostol 400-800ug/day endoscopic evidence
- H.pylori – ve pts with blocking H. pylori infection on low dose ASA+PPI have lower risk of ulcer complications vs clopidogrel alone

COXIBs: Selective cyclooxygenase 2 inhibitors
- Drug interactions
- DU:duodenal ulcer
- H2RA: H2-receptor antagonist. NSAIDs: nonsteroidal anti-inflammatories
- OTC: Over the counter
- PPI: proton pump inhibitor
- PE: peptic ulcer disease
- UBT: urea breath test
- UGIB: upper GI bleed

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