Proton Pump Inhibitors and the Treatment of GERD, Dyspepsia, NSAID-associated Peptic Ulcer Disease
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Goals

• Assist you to identify potential clinical situations where proton pump inhibitor (PPI) prescribing may not be consistent with optimal drug therapy

• Identify key references and tools to assist in the optimal prescribing and use of PPIs

• Create an awareness of optimal drug therapy information from the Canadian Agency for Drugs and Technologies in Health (CADTH)
Objectives

Review the use of Proton Pump Inhibitors (PPIs) in the treatment of:
- GERD
- Dyspepsia
- Peptic ulcer disease (NSAID induced & *H. Pylori*)

Review evidence for following PPI issues:
- Efficacy of one PPI vs. another
- Double-dose PPI as initial therapy
- Role in asthma, laryngeal symptoms & chronic cough associated with GERD
Background

- Who is CADTH?
- What is COMPUS?
- How were the PPI evidence-based statements developed?
  - Process for identifying evidence-based optimal therapy
- Why focus on PPIs?
Who is CADTH?

- Health Technology Assessment
- Common Drug Review
- COMPUS
What is COMPUS?

Identify evidence-based optimal drug therapy

Evaluate current use & identify gaps

Provide strategies & tools

Support & encourage informed decision making

Build networks & partnerships
Stakeholders:

- Physicians, pharmacists, nurses, other allied health professionals
- Federal/Provincial/Territorial Governments
- Consumers
- Manufacturers
- Collaborators in Canada and internationally
Identifying the evidence

- Clinical Practice Guidelines (CPGs) & Consensus Documents (CDs)
- Extracted PPI–related recommendations and statements
- Compiled a synopsis of existing statements and recommendations
- Evaluated all relevant cited references (AMSTAR\textsuperscript{SR}, adapted SIGN 50 checklist \textit{RCT, cohort, observational})
- Identified & evaluated relevant new evidence not yet incorporated in the CPGs
Identifying optimal drug therapy

PPI Expert Review Panel reviewed results, decided on final wording, and voted on statements

Stakeholder feedback/input (preliminary scientific report containing statements and evidence posted on web)

Published scientific report March 2007

Developed tools/strategies to support implementation of Optimal Drug Therapy
PPI Expert Review Panel

BC  Dr. J. Rideout  Family Physician
AB  Dr. S. van Zanten  Gastroenterologist
AB  Dr. A. Thomson  Gastroenterologist
SK  Dr. M. Caughlin  Family Physician
SK  Dr. B. Schuster  Pharmacist
MB  Dr. L. Targownik  Gastroenterologist
ON  Dr. A. Holbrook  Pharmacologist
ON  Dr. M. Brouwers  Methodologist
ON  Ron Goeree  Health Economist
ON  Dr. M. Man-Son-Hing  Geriatrician
ON  Dr. J. Marshall  Gastroenterologist
NS  Pam McLean-Veysey  Pharmacist
Why focus on PPIs?

Adoption of optimal therapy would have an impact on a large number of Canadians.

Criteria included

- Over-or under-use of prescription medications
- Size of patient population
- Potential impact on health outcomes
- Cost-effectiveness
- Potential to effect change
- Benefit to multiple jurisdictions
- Measurable outcomes
Why focus on PPIs?

Commonly prescribed, potentially over-utilized

- Canada 2003 - 2004
  - PPI prescriptions dispensed increased by 15%
  - 2003 - 10.8 million
  - 2004 - 12.4 million

CADTH 2007
Background

Estimated total PPI retail pharmacy sales in Canada:

Year:
- 2000
- 2001
- 2002
- 2003
- 2004

Millions of Dollars:
- 600
- 800
- 1000
- 1200

Source: IMS HEALTH, CANADA. Reprinted with permission of IMS HEALTH, CANADA
Evidence for PPI Use in gastroesophageal reflux disease, dyspepsia and peptic ulcer disease

CADTH 2007
Canadian Dyspepsia Working Group Definition

“Dyspepsia is a symptom complex of epigastric pain or discomfort thought to originate in the upper gastrointestinal tract, and it may include any of the following symptoms: heartburn, acid regurgitation, excessive burping/belching, increased abdominal bloating, nausea, feeling of abnormal/slow digestion or early satiety.”

Van Zanten 2000
Five key decision points in the approach to patients with uninvestigated dyspepsia

1. Are there other possible causes for the symptoms?

2. Does patient have Alarm symptoms (VBAD) or >50 years of age?

3. Is the patient using NSAIDs (including ASA)?

4. Is the dominant symptom heartburn, acid regurgitation, or both?

5. Is the patient infected with *H. Pylori*?
Are there other possible causes for the symptoms?

- Cardiac
- Hepatobiliary
- Medication-induced
- Lifestyle
- Dietary indiscretion

Treat as appropriate

Van Zanten 2000
Example medications associated with dyspepsia/esophagitis

NSAIDS/ASA/COX2 inhibitors
acarbose (Glucobay®)
alcohol
alendronate (Fosamax®)
corticosteroids
iron

metformin (Glucophage®)
antiotics (erythromycin)
orlistat (Xenical®)
potassium
theophylline

Thomson 2002
Bazaldua 1999
# Herbs that may cause dyspepsia

<table>
<thead>
<tr>
<th>HERB</th>
<th>SIDE EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garlic</td>
<td>Stomach burning, nausea</td>
</tr>
<tr>
<td>Gingko</td>
<td>Mild GI disturbances</td>
</tr>
<tr>
<td>Saw palmetto</td>
<td>Upset stomach</td>
</tr>
<tr>
<td>Feverfew</td>
<td>GI disturbances</td>
</tr>
<tr>
<td>White willow</td>
<td>Possible ADR similar to salicylates</td>
</tr>
</tbody>
</table>

Thomson 2002  
Bazaldua 1999
Lifestyle modifications to consider

- Small frequent meals
- Elevate head of bed
- Avoid tight fitting clothes
- Avoid laying down for 2-3 hours after eating
- Stop/reduce smoking, alcohol & caffeine
- Avoid irritating foods that precipitate event
- Lose weight/maintain an ideal weight
- Review medications
- Stress reduction

Thomson 2002
Kaltenbach 2006
Heidelbaugh 2003
OTCs for dietary indiscretion, mild-intermittent symptoms

**Antacids** limited evidence

- Dose of antacids is based on acid-neutralizing capacity of individual products
- Works fast (5-15 minutes)
- Frequent dosing, volume of liquid and taste can be a challenge
  - constipating = calcium, aluminum
  - diarrhea = magnesium
- Mg/Al antacids eg. Maalox, Mylanta preferred as constipating effect of Al$^{+2}$ counterbalanced by laxative effect of Mg$^{+2}$
- Consider concurrent clinical conditions & convenience (e.g. renal failure & use of Mg and Al containing antacids)

*Thomson 2002*
OTCs for dietary indiscretion, mild-intermittent symptoms

**H2RAs (Famotidine Pepcid AC, Complete, ranitidine Zantac)**

- Symptom relief similar to antacids, but takes 1 hour for effect
- duration of effect is longer
- Famotidine 10mg - ranitidine 75mg 30 tablets ≥$12 (generic <$10)
- Famotidine 10mg/Ca Carb/MgOH (Pepcid Complete®) 10 tabs $9
- Famotidine 20mg, ranitidine 150mg – pkg size ≤ 30 tabs

*if on a regular H2RA or PPI, can use an OTC product for occasional symptoms related to dietary indiscretion

Thomson 2002
Does patient have alarm symptoms (VBAD) or is patient >50yrs?

Refer back to physician when...

Age > 50 or alarm features

- Vomiting
- Bleeding/anemia
- Abdominal mass/unexplained weight loss
- Dysphagia

Van Zanten 2000
Is the patient using NSAIDs (including ASA)?

- **If on NSAID**, STOP therapy
- **If symptoms resolve & still need analgesic/anti-inflammatory**
  - Avoid NSAID, if possible (acetaminophen)
  - If NSAID must be used:
    - lowest dose
    - shortest duration

Van Zanten 2000
Is the patient using NSAIDs (including ASA)?

**If NSAID must be continued**

- For treatment of NSAID induced ulcer; standard dose PPI x 4-8 weeks provides higher healing rates than H2RAs & misoprostol 800mcg/day
  
  - Overall success rate in study of omeprazole 20mg, 40mg, and ranitidine 300mg daily (n=541):
    - Omeprazole 40mg: 79%
    - Omeprazole 20mg: 80%
    - Ranitidine: 63%
  
  - Overall success rate in study of omeprazole 20mg, 40mg, and misoprostol 800mcg daily (n=935):
    - Omeprazole 40mg: 75%
    - Omeprazole 20mg: 76%
    - Misoprostol: 71%

NS \ p<0.001, **NNT = 6 (95% CI: 4-13)**

CADTH 2007
Is the patient using NSAIDs (including ASA) ?

Do not need double dose PPI

- 2 RCTs $n=1476$: double dose omeprazole was not superior to single dose, both doses more efficacious than H2RA and misoprostol

Different PPIs produce similar healing rates for NSAID-associated ulcer.

- 1 systematic review: 3 RCTs allowed for indirect comparison of healing rates:
  - Omeprazole: 84-93%
  - Lansoprazole: 81-93%

CADTH 2007
McDonagh 2005
NSAID ulcer prophylaxis

Secondary prevention of gastric and duodenal ulcers:

- **Standard-dose PPIs** are more efficacious than standard-dose H2RA
  - NNT \( \text{GU} = 10 \) (95% CI: 8-17)
  - NNT \( \text{DU} = 27 \) (95% CI: 25-217)

- **Standard-dose PPIs** have similar efficacy to misoprostol 400-800mcg/day
  - No significant differences in terms of DU and GU relapse at 6 months
Who should be considered for NSAID prophylaxis?

- Prior history of GI event (ulcer, hemorrhage)
- Age >60 years
- High NSAID dosage (>2x normal dose)
- Patients on warfarin and NSAID
- Patients on corticosteroid and NSAID

All patients taking NSAIDS do not require prophylaxis.
Is the dominant symptom heartburn or acid regurgitation?

“A burning feeling rising from the stomach or lower chest towards the neck”
GERD/Eosophagitis definitions

- **Uninvestigated GERD**: dominant symptoms of heartburn and/or regurgitation which may be associated with other symptoms such as epigastric pain/discomfort and not investigated by endoscopy (or upper GI series)

- **Erosive esophagitis**: the presence of reflux symptoms and any length of **mucosal break** in the esophagus as a result of gastroesophageal reflux

- **Endoscopy-negative reflux disease (ENRD)**: applies to individuals with GERD who have normal endoscopy results while off treatment

Armstrong 2005
Vakil 2006
CADTH 2007
GERD treatment

PPIs or H2RAs?

Although H2RA therapy is effective in managing many patients, standard dose PPIs are superior to H2RAs in the initial & maintenance management of uninvestigated GERD and erosive esophagitis.

PPIs have a similar adverse event rate (generally minor) as H2RAs.
Uninvestigated GERD initial therapy

Standard-dose PPIs, for up to four weeks, are more efficacious than H2RAs for improvement of reflux symptoms in uninvestigated GERD.

5 RCTS, N=1896

Patient pop’n: most had at least moderate heartburn

Outcomes:

- Heartburn relief
- Time to relief, regurgitation, epigastric pain

Symptom relief with initial therapy @ 4-8 weeks:

- PPIs 55-75%  Higher healing rates @ 8 wks
- H2RAs 27-58%, p<0.001
- NNT 4 -6 (95% CI 3-15) @ 4-8 weeks

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Uninvestigated GERD maintenance therapy

PPI therapy in uninvestigated GERD is more efficacious than H2RAs for control of symptoms, for up to six months.

3 RCTs, duration 20 weeks to 1 year, N=3056

Patients with heartburn dominant symptoms

1-year study, pantoprazole 20 mg daily vs ranitidine 150 mg bid

- Complete symptom control at 6 months
  - Pantoprazole 71%
  - Ranitidine 56% NNT 7 (95% CI 4-23)
- Complete symptom control at 12 months
  - Pantoprazole 77%
  - Ranitidine 59% NNT 6 (95% CI 4-13)
- At 12 months: Proportion with sufficient symptom control and relapse rates in patients who were controlled at 8 weeks
  - No difference between PPI and H2RA

2 shorter studies showed decreased relapse rate and better symptom control with PPIs.

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Alternates to daily PPI maintenance for GERD

• Continued PPI therapy is more efficacious than step-down to H2RAs in uninvestigated GERD and erosive esophagitis.

• Alternatives (PPI discontinuation, H2RAs, on demand dosing) to long-term regular use of standard dose PPIs for GERD may be appropriate in select patients.

• ≈20% of uninvestigated GERD patients remain asymptomatic off therapy for up to 6 months after a successful initial course (4-8 wks treatment) with a PPI or H2RA.
Uninvestigated GERD step down to H2RA

Patients who have completed an initial course of PPI, continued PPI is more efficacious than step-down to H2RA for symptom relief.

One RCT using lansoprazole 30 mg once daily and ranitidine 150 mg twice daily.

Outcome: Heartburn relief at 20 weeks

- PPI: 82%
- PPI x 8 weeks, H2RA x 12 weeks: 67%
- NNT 7 (95%CI 4, 20)

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On demand PPI therapy?

- More efficacious than placebo (uninvestigated GERD, ENRD)
- More efficacious than continuous standard dose H2RA (uninvestigated GERD)
- Less efficacious than continuous PPI (uninvestigated GERD, EE)
The two latter statements were supported by 1 RCT (n=2,156) that compared continuous std dose PPI, continuous std dose H2RA, and std dose PPI taken on-demand over 6 months in patients heartburn as predominant symptom:

- Proportion w/o heartburn at 6 months
  - Continuous PPI: 72.2%
  - On-demand PPI: 45.1%
  - Continuous H2RA: 32.5%

- Proportion at least ‘very satisfied’ at 6 months
  - Continuous PPI: 82.2%
  - On-demand PPI: 75.4%
  - Continuous H2RA: 33.5%

- On-demand patients used 35% less drug on average than continuously-dosed patients

NNT (95% CI) = 4 (3, 5)
NNT (95% CI) = 8 (6, 14)
p<0.01
p<0.0001
Is the patient infected with *Helicobacter Pylori*?

First-Line Triple Therapy

- “1-2-3”: **1** week, **2** times a day, **3** drugs
- Currently approved 7 day regimens
  - PPI
    - + clarithromycin (Biaxin®)
    - + amoxicillin or metronidazole

First-Line Quadruple Regimens

- PPI twice daily + BMT four times daily (bismuth+metronidazole+tetracycline)
- Compliance is critical for HP eradication treatment success

Van Zanten 2000
HP common questions

**Is follow-up acid suppression needed?**

- Not generally indicated for uncomplicated duodenal ulcer
- Exceptions
  - gastric ulcers
  - patients that remain symptomatic
  - complicated patients with large or refractory ulcers
    - ensure ulcer healing & HP eradicated
  - Maintenance anti-secretory therapy for patients at high risk for recurrence / bleeding
    - e.g. high acid-secretory condition

References:
- CADTH 2007
- Van Zanten 1997
- Gisbert 2005
- Tytgat 1998
- Hunt 1998
**HP common questions**

**Is follow-up testing to confirm eradication required?**

- Repeat testing generally not recommended
- Exceptions: patients that remain symptomatic, bleeding/perforated ulcers, MALT lymphoma or gastric cancer
- Cannot use serology

**What approach for HP eradication treatment failure?**

Use a different first-line therapy other than one used initially or

PPI + BMT 14 days

**Does drug therapy impact Urea Breath Test for HP results?**

*H. pylori* testing possible false negatives:

- discontinue abx/bismuth 4wks prior \[\text{suppress}\]
- discontinue acid suppression 1wk \[\text{HP}\]

Van Zanten 2000
Hunt 1999
Hunt 1998
Objectives

Review the use of Proton Pump Inhibitors (PPIs) in the treatment of

- GERD
- Dyspepsia
- Peptic ulcer disease (NSAID induced & *H. Pylori*)

Review evidence for following PPI issues

- Efficacy of one PPI vs. another
- Double-dose PPI as initial therapy
- Role in asthma, laryngeal symptoms & chronic cough associated with GERD
Which PPI should be used?

All PPIs are equally efficacious

Standard doses of PPIs may be used interchangeably when initiating therapy because there are no clinically important differences among the various PPIs in the treatment of most acid-related GI conditions.

### PPI Standard doses

<table>
<thead>
<tr>
<th>PPI</th>
<th>Brand Name</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Losec®</td>
<td>20mg daily</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>Pariet®</td>
<td>20mg daily</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Pantoloc®</td>
<td>40mg daily</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Prevacid®</td>
<td>30 mg daily</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>Nexium®</td>
<td>20mg daily</td>
</tr>
</tbody>
</table>

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Evidence-based support
All PPIs are equally efficacious

GERD/ENRD/Esophagitis
- 6 good quality systematic reviews-no clinically important differences in standard doses PPIs
- Isolated exceptions, majority showed no differences
- Comparisons showing some degree of difference involved non-equivalent comparisons (e.g. high dose vs. standard dose)

H. pylori Eradication
- 7 systematic reviews\(^5\) good quality: PPIs have similar efficacy when used in triple therapy regimens
Evidence-based Support
All PPIs are equally efficacious

**NSAID Ulcer Prophylaxis**
- 1 good quality systematic review \(^7\) RCTs (indirect comparisons formal stat methods not employed), and 1 RCT direct comparison: different PPIs reduce ulcer risk to a similar degree (the only direct comparison was of omeprazole vs pantoprazole)

**NSAID Ulcer Healing**
- 1 good quality systematic review \(^3\) RCTs (indirect comparisons formal stat methods not employed): similar healing rates for the PPIs that have been studied (omeprazole & lansoprazole)
Evidence-based limitations
All PPIs are equally efficacious

- Isolated studies may show superiority, balance against weight of evidence
- Caution for comparisons between non-equivalent doses of PPIs, e.g. omeprazole 20mg vs. esomeprazole 40mg
- No evidence regarding safety and efficacy of switching to a different PPI in patients successfully treated with a given PPI
- Not all comparisons have been made for all indications
- Official indications may be more limited in scope e.g. apo-omeprazole not officially indicated for H. pylori eradication
- Balance evidence against need for patient individualization
Bottom line
All PPIs are equally efficacious

- There are no clinically important differences among standard doses, or equivalent doses of PPIs in the initial treatment of most acid related GI conditions
- In most circumstances the data suggests clinicians may interchange PPIs with confidence
- The equality of PPIs is supported by the majority of the available literature
**Implications to practice**

Cost savings to the patient/society

Simplify prescribing by focusing on lowest cost PPI.

<table>
<thead>
<tr>
<th>Standard Dose PPIs</th>
<th>Generic Omeprazole 20mg Daily</th>
<th>Rabeprazole (Pariet®) 20mg Daily</th>
<th>Pantoprazole (Pantoloc®) 40mg Daily</th>
<th>Lansoprazole (Prevacid®) 30mg Daily</th>
<th>Esomeprazole (Nexium®) 20mg Daily</th>
<th>Omeprazole (Losec®) 20mg Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Price</td>
<td>$1.25</td>
<td>$1.30</td>
<td>$1.90</td>
<td>$2.00</td>
<td>$2.10</td>
<td>$2.20</td>
</tr>
<tr>
<td>Approximate Monthly Price</td>
<td>$43.00</td>
<td>$44.40</td>
<td>$61.20</td>
<td>$64.00</td>
<td>$66.80</td>
<td>$69.60</td>
</tr>
</tbody>
</table>

Generic omeprazole 20mg and rabeprazole (Pariet®) 20mg are the cheapest “standard” dose PPIs on the Canadian market. Using a PPI that costs $1.40/day vs. $2.20/day will save a patient almost $300 per year in drug costs.
Potential yearly savings
*Society/Patients*

Canada 2004 12.4 million PPI prescriptions

Imagine if 50% were changed from:

$2.20/day regimen $1.25/day regimen

0.95 cents saved/day x 30 days x 6.2 million prescriptions:

$176 million dollars/year
What dose of PPI?
More may not always be better

• High or double-dose PPI, as initial therapy, is no better than standard daily dose therapy in the management of erosive esophagitis

• Research Gaps: double dose in GERD patients with severe symptoms or in patients who remain symptomatic after an initial course of standard dose therapy

CADTH 2007
Evidence based support
More may not always be better

High or Double-dose PPIs for initial Rx Erosive Esophagitis

- 6 RCTs $^{N=1388}$: 2 RCTs very good quality, 1 good quality, 3 poor quality grade 2-4 esophagitis

- Majority of evidence: no benefit for initial treatment
- Limitation: small number of trials, all of poor quality, specifically addressed Grade 2-4 esophagitis (more severe)

Esomeprazole 40mg is approved dose for erosive esophagitis

- Some but not all trials of 40mg vs standard dose PPIs have shown benefit
- Clinical importance unclear

CADTH 2007
McDonagh 2005
Evidence based support
More may not always be better

Double-dose initial Rx NSAID-induced ulcer

- 2 RCTs n=1476: double dose omeprazole was not superior to single dose
- both standard and double doses more effective than H2RA (NNT=4-9) and misoprostol (NNT=6-8)

Do not need double-dose PPI

CADTH 2007
Bottom line

*Little evidence that more is better*

Doubling the standard daily dose of PPIs, as initial therapy, is no better than standard daily dose therapy.

**Standard dose should be the initial therapy.**
Double-dose PPI therapy may be considered if:

- Standard doses are not effective (e.g. after 2-4 weeks)
- Lack of response to standard dose PPI warrants:
  - **Reassessment of diagnosis**
  - **Ensure patient taking PPI properly**
- In hypersecretory conditions (e.g. Zollinger-Ellison syndrome, *H. pylori* eradication regimens and select patients post-GI bleed (4 weeks))
- **Double-dose PPI should be reassessed after 4-8 weeks**
## Implications to practice

### Cost savings

<table>
<thead>
<tr>
<th>Standard Dose PPIs</th>
<th>Generic omeprazole (Losec®) 20mg Daily</th>
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<td>$61.20</td>
<td>$64.00</td>
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<td>$69.60</td>
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<tr>
<td>High Dose PPIs</td>
<td>Esomeprazole 40mg Daily</td>
<td>Generic omeprazole 40mg Daily</td>
<td>Rabeprazole 20mg Twice Daily</td>
<td>Pantoprazole 40mg Twice Daily</td>
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<td>Daily Price</td>
<td>$2.10</td>
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<td>$80.80</td>
<td>$114.40</td>
<td>$120.00</td>
<td>$131.20</td>
</tr>
</tbody>
</table>

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**CADTH 2007**
PPIs: asthma, laryngeal symptoms & chronic cough use the right tool for the job

PPIs are not efficacious in the treatment of asthma, chronic cough and laryngeal symptoms that may be associated with GERD.
Evidence-based support

Asthma with concomitant GERD

One good quality systematic review (12 RCTs, n=432)

- PPI (omeprazole 20-80 mg) or H2RA did not improve FEV1, PEF, airway responsiveness or use of inhalers
- 1 RCT (omeprazole 40 mg vs placebo) reported improvement in nocturnal symptom score

CADTH 2007
Evidence-based support

Laryngeal symptoms with Reflux

One good quality systematic review (5 RCTs, n=247)

- **No significant effect** on laryngo-pharyngeal symptoms (e.g., cough, throat clearing, globus, hoarseness, sore throat)
Evidence-based support

Chronic cough with or without GERD

One good quality systematic review

Chronic cough ≥3 weeks without respiratory symptoms/signs or systemic illness

Cough score at various times

- No benefit of PPI vs. placebo

Limitations:

- Small pooled sample size: analysis likely underpowered
- Heterogeneity in study population
Bottom line PPIs: asthma, laryngeal symptoms & chronic Cough

PPI effective for treating GI disease
Current evidence would suggest they are not efficacious in improving asthma, laryngeal symptoms or chronic cough that may be associated with GERD.

The use of PPIs for this indication should be discouraged.
PPI Interventions & Tools

Physician Educational Materials
- Alternate Prescription Pad
- Newsletter “3 Questions to Ask When Starting a PPI”
- Self Audit Form
- Academic Detailing
- Interactive and Didactic Presentation
- Prescribing Aid

Pharmacists Materials
- Interactive and Didactic Presentation

Patient Education Materials
- Information Brochure / Alternate Prescription Pad
More than 1/4 of Canadians have symptoms caused by the acid in their stomach. Symptoms can include heartburn, indigestion, bloating and a feeling of fullness.

Whether or not you have been prescribed a medication, there are things you can do that may help reduce your symptoms.

- Avoid foods that worsen your symptoms, such as:
  - coffee
  - chocolate
  - overly spicy or high-fat meals
  - acidic foods (e.g., tomatoes, lemons)
  - carbonated beverages
- Do not lie down for 2 to 3 hours after eating
- Do not wear tight-fitting clothing
- Stop or reduce the amount you smoke
- Elevate the head of your bed using blocks or books
- Eat smaller meals and chew food well
- Lose weight if appropriate

For full project information: www.cadth.ca

If your symptoms are mild or only occur once in a while, you may not need to take regular prescription medication. You can treat your symptoms whenever they occur using medications available without a prescription at your local pharmacy. There are two types of products you can use:

**Products That Neutralize Acid**
- Liquid or tablets (e.g., Gaviscon®, Maalox®, Tums®)
  - Works fast (5 to 15 minutes), lasts for 1 to 2 hours
  - Pennies per dose, especially using store brand antacids

**Products That Stop Acid Production**
- Zantac®, Pepcid® or generic ranitidine or famotidine
  - Takes ~ 1 hour for effect, lasts for up to 12 hours
  - Can cost as little as 25 cents per dose

Consult with your Pharmacist for the best option for you

If your symptoms don’t go away within 2 weeks, or if they get worse: Contact Your Doctor

Doctor Signature: ____________________________

Pharmacist Signature: ________________________
Which PPI should I choose? What dose should I start at? What won’t a PPI treat?

Three Questions

Which PPI should I choose?

At what dose should I start?

What won’t a PPI treat?

PPI Pharmacology:
PPIs suppress gastric acid by irreversibly inhibiting the H+–K+ATPase or the “proton pump” that secretes acid into the lumen of the stomach. Since all five of the PPIs currently on the Canadian market have the same mechanism of action, it is expected that all would produce similar results at equivalent doses. Due to the irreversible binding of PPIs, subtle differences in pharmacokinetic properties may not significantly affect duration of action since acid production requires regeneration of proton pumps. 

Evidence-based Support:
For gastroesophageal reflux disease (GERD), including both endoscopically negative reflux disease (ENRD) and erosive, no clinically important differences were found at standard doses of PPIs. To robust evidence supporting the conclusion includes the quality systematic reviews. While there are isolated observations, the majority of comparisons of PPIs for GERD showed no significant differences in healing rates or duration up to one year studies.

For H. pylori eradication, PPIs have similar efficacy when used in triple-therapy regimens. Superiority of any one PPI was not suggested by any of the seven systematic reviews.

For NSAID ulcer prophylaxis, indirect comparisons from a good quality systematic review showed no clinically significant differences between the PPIs.

For NSAID ulcer healing, the agents in a head to head should also be recognized that of PPI use indications for each brand of PPI may vary.

Implications for Clinical Practice:
With the evidence indicating that there are no clinically important differences among the PPIs for the treatment of common acid-related GI conditions, practitioners may choose to use the lower cost alternatives when prescribing PPIs, while not compromising quality of care.

Price Comparison of Standard Once Daily Dose PPIs

<table>
<thead>
<tr>
<th>PPI</th>
<th>Unit Dose</th>
<th>Cost/1000mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>20 mg</td>
<td>$1.25/day</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>20 mg</td>
<td>$1.30/day</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40 mg</td>
<td>$1.95/day</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>40 mg</td>
<td>$2.00/day</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30 mg</td>
<td>$2.00/day</td>
</tr>
<tr>
<td>Nexium</td>
<td>20 mg</td>
<td>$1.10/day</td>
</tr>
<tr>
<td>Losartan</td>
<td>20 mg</td>
<td>$1.30/day</td>
</tr>
</tbody>
</table>
Quick reference prescribing aid

Three Questions to Ask When Considering a PPI

1. **Which PPI should I choose?**
   On initial therapy there are no clinically important differences among equivalently-dosed PPIs in the treatment of most acid-related GI conditions.

2. **At what dose should I start?**
   Studies comparing standard doses of PPI to high doses have not shown superiority of starting with the higher dose. Standard-dose therapy should be the initial therapy for all patients.

3. **What won’t a PPI treat?**
   Current evidence suggests PPIs are not efficacious in improving asthena, laryngeal symptoms or chronic cough that may be associated with GERD.

For full project information, visit the CADTH web site:

www.cadth.ca

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**Canadian Agency for Drugs and Technologies in Health**

**Agence canadienne des médicaments et des technologies de la santé**
Role of pharmacist

• Referral to family physician  (Remember Vbad)
• Identify drug and herbal causes of dyspepsia
• Treatment consistent with best practices
• Tailor drug therapy
• Medication information
• Monitor response/side effects & drug interactions
• Seamless care
• Ensure therapy reassessed
Summary

- Standard doses of PPIs may be used interchangeably for initial therapy because there are no clinically important differences among the PPIs in most acid-related GI conditions.
- Standard doses are sufficient for initial therapy in most conditions (exceptions: HP regimens, upper GI bleed).
- PPIs are not efficacious in the treatment of asthma, chronic cough, and laryngeal symptoms that may be associated with GERD.
Summary

- Although H2RA therapy is effective in managing many patients, standard-dose PPIs are superior to H2RAs for initial and maintenance therapy of uninvestigated GERD and erosive esophagitis and the initial treatment of ENRD.
- Patients with uncomplicated duodenal ulcers don’t require continuation of PPI therapy after HP eradication.
- Standard-dose PPIs and misoprostol 400-800mcg/day have similar efficacy in the prevention of NSAID-associated ulcers.
Questions?
References


References


References


References


Additional background slides
Factors influencing drug coverage

There are many factors that influence decisions to include a drug on a formulary:

- Patient population
- Clinical efficacy
- Cost-effectiveness
- Resources available/Budget Impact

Choices:

Full Benefit, Restricted Benefit, Not a benefit
The PPI economic component

The economic component of the PPI project compared expected costs and outcomes of various primary care strategies for the following:

- Heartburn in patients with moderate-to-severe, uninvestigated GERD
- Patients with uninvestigated dyspepsia
- Prevention of GI complications in patients using NSAIDs
Economic terminology

**Quality Adjusted Life Year (QALY):**

- Outcome measure that incorporates both quantity of life (mortality) and health-related quality of life (morbidity)
- Quantity – how long person lives
- Quality – factor that represents a preference for a health state
  - one year of perfect health = one QALY
  - one year less than perfect health < one QALY
  - death = zero

\[ \text{i.e., a person in perfect health (quality weight=1) for 10 years followed by 10 years in a health state with a quality weight of 0.50 would have achieved 15 QALYs (}10 \times 1 + 10 \times 0.5)\]

Berger 2003
Medicinenet.com
Economic terminology

How much is a QALY worth?

• There is no simple answer
• The debate on appropriate value (i.e. $50,000) of a QALY continues*
• Resource allocation decisions must take this question into consideration

## Economic conclusions

**Prevention of GI complications associated with NSAID use**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (C$)</th>
<th>Incr Cost</th>
<th>Effectiveness (QALY)</th>
<th>Incr Eff</th>
<th>Incr C/E (ICER)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID alone</td>
<td>366</td>
<td></td>
<td>14.7858</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID+PPI</td>
<td>529</td>
<td>163</td>
<td>14.7883</td>
<td>0.002555</td>
<td>63,835</td>
</tr>
<tr>
<td>NSAID+H2RA</td>
<td>610</td>
<td>81</td>
<td>14.7884</td>
<td>0.000039</td>
<td>2,112,682</td>
</tr>
</tbody>
</table>

Incr=incremental; QALY=quality-adjusted life year; Incr Eff=incremental effectiveness

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**Economic Models 2007**

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**Canadian Agency for Drugs and Technologies in Health**

**Agence canadienne des médicaments et des technologies de la santé**
Economic conclusions

Heartburn in patients with moderate to severe uninvestigated GERD
Population - Uninvestigated GERD

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Expected 1yr cost per patient</th>
<th>Expected QALYs</th>
<th>Incremental cost per QALY(^1) (Cdn$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: PPI on-demand</td>
<td>$635</td>
<td>0.899</td>
<td>--</td>
</tr>
<tr>
<td>B: H2RA on demand</td>
<td>$665</td>
<td>0.889</td>
<td>Dominated by A</td>
</tr>
<tr>
<td>C: PPI with step-down</td>
<td>$754</td>
<td>0.903</td>
<td>Extendedly dominated</td>
</tr>
<tr>
<td>H2RA maintenance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D: H2RA maintenance</td>
<td>$789</td>
<td>0.896</td>
<td>Dominated by C</td>
</tr>
<tr>
<td>E: PPI maintenance</td>
<td>$816</td>
<td>0.905</td>
<td>$27,848</td>
</tr>
</tbody>
</table>

\(^1\)Relative to the next less costly non-dominated strategy
**Economic conclusions**

Patients with non-heartburn predominant uninvestigated dyspepsia

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost</th>
<th>Incremental Cost</th>
<th>ICER†††</th>
</tr>
</thead>
<tbody>
<tr>
<td>B) Without dominated options (simple or extended)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empirical Antisecretery Therapy (omeprazole)</td>
<td>219</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test and treat all (omeprazole)</td>
<td>239</td>
<td>20</td>
<td>10,004</td>
</tr>
<tr>
<td>Prompt Endoscopy (H₂RA)</td>
<td>1222</td>
<td>982</td>
<td>205,643</td>
</tr>
<tr>
<td>Prompt Endoscopy (PPI)</td>
<td>3083</td>
<td>1862</td>
<td>688,990</td>
</tr>
</tbody>
</table>

H₂RA=histamine-2 receptor antagonists; ICER=international cost-effectiveness ratio; PPI=proton pump inhibitor; SF=symptom free
††† Incremental cost-effectiveness ratio (incremental cost per QALY)
ENRD – Initial Therapy

PPIs are more efficacious than H2RAs as initial therapy for improvement of heartburn symptoms at 4 weeks in patients with ENRD. However, PPIs are not superior to H2RAs in terms of improving quality of life.

One SR included 4 RCTs (N=960)

- RR for heartburn persistence = 0.78 (95% CI: 0.62-0.97)
- Pooled heartburn relief rates in the 4 trials:
  - Standard dose PPIs: 53%
  - H2RAs: 42%
- 2 RCTs measured QoL: No significant difference in reflux dimension or total score of Gastrointestinal Symptoms Rating Scale (GSRS)
## Economic conclusions

Heartburn in patients with moderate to severe uninvestigated GERD
Population - ENRD

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Expected 1yr cost per patient</th>
<th>Expected QALYs</th>
<th>Incremental cost per QALY(^1) (Cdn$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: H2RA on demand</td>
<td>641</td>
<td>0.890</td>
<td>--</td>
</tr>
<tr>
<td>B: PPI on demand</td>
<td>660</td>
<td>0.898</td>
<td>$2,505</td>
</tr>
<tr>
<td>C: PPI with step-down H2RA maintenance</td>
<td>770</td>
<td>0.902</td>
<td>Extendedly Dominated</td>
</tr>
<tr>
<td>D: H2RA maintenance</td>
<td>772</td>
<td>0.897</td>
<td>Dominated by C</td>
</tr>
<tr>
<td>E: PPI maintenance</td>
<td>827</td>
<td>0.904</td>
<td>$26,986</td>
</tr>
</tbody>
</table>

\(^1\)Relative to the next less costly non-dominated strategy

CADTH Economic Models 2007
Erosive esophagitis - initial therapy

**PPIs are more efficacious than H2RAs for improving symptoms and healing of erosive esophagitis.**

2 SRs and 5 RCTs N= 4310

**Outcomes: 1 week – 6 months**

- Healing of erosions
  - H2RAs
    - 4 weeks range of 26% - 54%
    - 8 weeks or more range of: 35-76%
  - PPIs
    - 4 weeks 56 – 74%
    - 8 weeks or more 71% - 90%
- Symptom relief
- Similar rates as for healing
Erosive esophagitis - maintenance

Long-term maintenance PPI therapy (i.e., up to 12 months) in erosive esophagitis is more efficacious than H2RAs for prevention of symptomatic and endoscopic relapse.

Patients resistant to H2RAs: 1RCT N=98

• Proportion with symptomatic and endoscopic remission at 12 months:
  • Omeprazole 40 mg daily 67%
  • Ranitidine 300 mg bid 10% (p<0.0001)
Erosive esophagitis - maintenance

*Long-term PPI therapy is more efficacious than H2RAs for erosive esophagitis complicated by strictures.*

3 RCTs, N=561, Duration 6 months- 1 year

**Outcomes:** redilatation, dysphagia relief

- Results in 2 smaller studies: PPIs lower rates of redilatation and greater reduction in dysphagia but non-significant
- The larger study (n=366) found a significant reduction in redilatation and symptom relief however the rates were similar to other studies: dysphagia relief in 76% of PPI patients vs. 64% of H2RA patients, p<0.05
- Consensus thought is that PPIs are better for this patient population
**Economic conclusions**

Heartburn in patients with moderate to severe uninvestigated GERD Population - erosive esophagitis

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Expected 1yr cost per patient</th>
<th>Expected QALYs</th>
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<tbody>
<tr>
<td>A: PPI on-demand</td>
<td>537</td>
<td>0.902</td>
<td>--</td>
</tr>
<tr>
<td>B: H2RA on-demand</td>
<td>560</td>
<td>0.895</td>
<td>Dominated by A</td>
</tr>
<tr>
<td>C: PPI with step-down H2RA maintenance</td>
<td>692</td>
<td>0.907</td>
<td>$33,692</td>
</tr>
<tr>
<td>D: H2RA maintenance</td>
<td>717</td>
<td>0.901</td>
<td>Dominated by C</td>
</tr>
<tr>
<td>E: PPI maintenance</td>
<td>776</td>
<td>0.909</td>
<td>$44,168</td>
</tr>
</tbody>
</table>

\(^1\)Relative to the next less costly non-dominated strategy

*CADTH Economic Models 2007*
Erosive esophagitis step-down

In patients with erosive esophagitis who have completed an initial course of PPIs, half-dose PPI maintenance therapy is more efficacious than step-down to H2RAs for preventing relapse and providing improvement of symptoms.

One systematic review of 4-6 trials. N=831-1156

Proportion with relapse of esophagitis at 24-52 weeks:
- PPI half dose 39%
- H2RA 66%; RR=0.57; (95% CI 0.47, 0.69)
- NNT (95% CI) 3 (2 - 5)

Proportion with relapse of symptoms at 24-52 weeks:
- PPI half dose 31%
- H2RA 44%; RR=0.55; (95% CI 0.47, 0.65)
- NNT (95% CI) 4 (3 - 5)
(ASTRONAUT Study): 541 patients with DU, GU, or >10 GI erosions receiving NSAIDs treated with omeprazole 20mg or 40mg, or ranitidine 300mg daily.

Results for omeprazole 20mg vs. ranitidine:

<table>
<thead>
<tr>
<th>Outcome (at 8 weeks)</th>
<th>Tx failures (Ome vs. Ran)</th>
<th>RR of failure (95% CI)</th>
<th>NNT (95% CI) for success</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Treatment Failure’</td>
<td>20% vs. 37%</td>
<td>0.55 (0.38-0.78)</td>
<td>6 (4, 13)</td>
</tr>
<tr>
<td>DU healing</td>
<td>8% vs. 19%</td>
<td>0.44 (0.12-1.5)</td>
<td>9 (NNH 4, NNT 24)</td>
</tr>
<tr>
<td>GU healing</td>
<td>16% vs. 36%</td>
<td>0.44 (0.24-0.82)</td>
<td>5 (3, 17)</td>
</tr>
</tbody>
</table>

Results for double dose vs. standard dose omeprazole:

- Treatment failure: 21% vs. 20%, p>0.05 (NS)
- DU persistence: 12% vs. 8%, p>0.05 (NS)
- GU persistence: 13% vs. 16%, p>0.05 (NS)

Yeomans 1998
What about a COX2 vs a NSAID?

There is no difference in ulcer reoccurrence and bleeding rates between COX-2 selective NSAIDs and the combination PPI and conventional NSAIDs in patients with previous NSAID-associated upper GI bleeding

• One RCT comparing 6 months of celecoxib 200 bid vs. diclofenac 75 mg bid plus omeprazole 20 mg qd in patients with previous GI hemorrhage on an NSAID
  • no difference in risk of recurrent bleeding or endoscopic ulcer at 6 months

• Second RCT - celecoxib 200 qd vs. lansoprazole 30 mg qd plus naproxen 250 tid for 24 weeks
  • No difference in re-occurrence of ulcer complications