Pharmacist Presentation

Canadian Agency for Drugs and Technologies in Health | Agence canadienne des médicaments et des technologies de la santé

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

Presenter

Title

Affiliation

Date

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Statement of disclosure

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

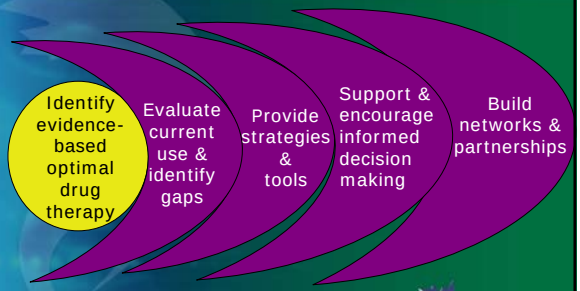
Background

- **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?



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Stakeholders:

- Physicians, pharmacists, nurses, other allied health professionals
- F/P/T Governments
- Consumers
- Manufacturers
- Collaborators in Canada and internationally

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

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^{SR}, adapted SIGN 50 checklist $^{RCT, cohort, observational}$)
- 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

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

*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 X 1 + 10 X 0.5)**

Berger 2003

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

Hirth 2000

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**

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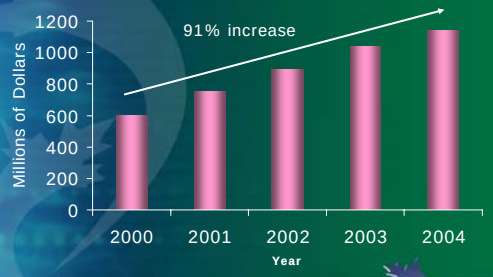
Background

Estimated total PPI retail pharmacy sales in Canada:



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Evidence for PPI Use in gastroesophageal reflux disease, dyspepsia and peptic ulcer disease

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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

Economic conclusions

Patients with non-heartburn predominant uninvestigated dyspepsia

Strategy	Cost	Incremental Cost	ICER†††
B) Without dominated options (simple or extended)			
Empirical Antisecretory Therapy (omeprazole)	219		
Test and treat all (omeprazole)	239	20	10,004
Prompt Endoscopy (H_2RA)	1222	982	205,643
Prompt Endoscopy (PPI)	3083	1862	688,990

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)

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 >50years 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*?

Van Zanten 2000

Are there other possible causes for the symptoms?

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

Treat as appropriate

Van Zanten 2000

Medications associated with dyspepsia

NSAIDS/ASA/COX2 inhibitors

acarbose (Glucobay®)

alcohol

alendronate (Fosamax®)

corticosteroids

iron

metformin (Glucophage®)

antibiotics (erythromycin)

orlistat (Xenical®)

potassium

theophylline

Thomson 2002
Bazaldua 1999

Herbs noted to have side effects that may be confused with dyspepsia

HERB	SIDE EFFECT
Garlic	Stomach burning, nausea
Gingko	Mild GI disturbances
Saw palmetto	Upset stomach
Feverfew	GI disturbances
White willow	Possible ADR similar to salicylates

Thomson 2002
Bazaldua 1999

Reduce or Eliminate Factors that Affect Dyspepsia

- 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

- 10-20ml/ 2-4 tabs pc & HS prn (higher doses in GERD)
- 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

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*
- *Pepcid® 10mg-Zantac® 75mg 30 tablets ⩾$12 (generic <$10)*
- *Pepcid Complete®(Famotidine 10mg/Ca Carb/MgOH) 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

V*omiting*

B*leeding/anemia*

A*bdominal mass/unexplained weight loss*

D*ysphagia*

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$^{\text{healed ulcer, <5 erosions, ≤mild dyspepsia}}$ in study of omeprazole 20mg, 40mg, and ranitidine 300mg daily (n=541):
    - Omeprazole 40mg: 79%
    - Omeprazole 20mg: 80%
    - Ranitidine: 63%

    NS; p<0.001, **NNT = 6 (95% CI: 4-13)**
  - Overall success rate$^{\text{healed ulcer, <5 erosions, ≤mild dyspepsia}}$ in study of omeprazole 20mg, 40mg, and misoprostol 800mcg daily (n=935):
    - Omeprazole 40mg: 75%
    - Omeprazole 20mg: 76%
    - Misoprostol: 71%

    NS; NS

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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%

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McDonagh 2005

NSAID ulcer prophylaxis

Secondary prevention of gastric and duodenal ulcers:

- **Standard-dose PPIs are more efficacious than standard-dose H2RA**
  - NNT ^{GU}=10 (95% CI: 8-17)
  - NNT ^{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

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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.

Lanza 1998

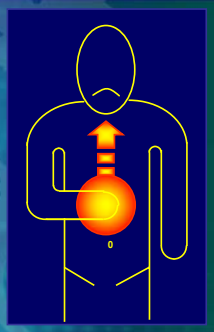
Economic conclusions

Prevention of GI complications associated with NSAID use

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

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

Is the dominant symptom heartburn or acid regurgitation?



"A burning feeling rising from the stomach or lower chest towards the neck"

GERD / Esophagitis 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 gastroesopageal 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.

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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:

Higher healing rates @ 8 wks

- PPIs 55-75%
- 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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Economic conclusions

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

Strategy	Expected 1yr cost per patient	Expected QALYs	Incremental cost per QALY[1] (Cdn$)
A: PPI on-demand	$635	0.899	--
B: H2RA on demand	$665	0.889	Dominated by A
C: PPI with step-down H2RA maintenance	$754	0.903	Extendedly dominated
D: H2RA maintenance	$789	0.896	Dominated by C
E: PPI maintenance	$816	0.905	$27,848

[1]Relative to the next less costly non-dominated strategy

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)

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

Economic conclusions

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

Strategy	Expected 1yr cost per patient	Expected QALYs	Incremental cost per QALY[1] (Cdn$)
A: H2RA on demand	641	0.890	--
B: PPI on demand	660	0.898	$2,505
C: PPI with step-down H2RA maintenance	770	0.902	Extendedly Dominated
D: H2RA maintenance	772	0.897	Dominated by C
E: PPI maintenance	827	0.904	$26,986

[1]Relative to the next less costly non-dominated strategy

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

Strategy	Expected 1yr cost per patient	Expected QALYs	Incremental cost per QALY[1] (Cdn$)
A: PPI on-demand	537	0.902	--
B: H2RA on-demand	560	0.895	Dominated by A
C: PPI with step-down H2RA maintenance	692	0.907	$33,692
D: H2RA maintenance	717	0.901	Dominated by C
E: PPI maintenance	776	0.909	$44,168

[1]Relative to the next less costly non-dominated strategy

GERD treatment

Step down therapy to H2RA?

- 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

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

One RCT

Outcome: Heartburn relief at 20 weeks

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

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)

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)

On demand PPI therapy?

- 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% } NNT (95% CI) = 4 (3, 5)
    - On-demand PPI: 45.1% } NNT (95% CI) = 8 (6, 14)
    - Continuous H2RA: 32.5%
  - Proportion at least 'very satisfied' at 6 months
    - Continuous PPI: 82.2% } p<0.01
    - On-demand PPI: 75.4% } p<0.0001
    - Continuous H2RA: 33.5%
  - On-demand patients used 35% less drug on average than continuously-dosed patients

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)

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

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
- 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 HP testing results?

H. pylori testing possible false negatives:

- discontinue abx/bismuth 4wks prior } suppress
- discontinue acid suppression 1wk } 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 inter-changeably 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

Omeprazole	Rabeprazole	Pantoprazole	Lansoprazole	Esomeprazole
Losec®	Pariet®	Pantoloc®	Prevacid®	Nexium®
20mg daily	20mg daily	40mg daily	30 mg daily	20mg daily

CADTH 2007

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

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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 [3RCTs] (indirect comparisons [formal stat methods not employed]):*
  similar healing rates for the PPIs that have been studied (omeprazole & lansoprazole)

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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.

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

Generic omeprazole 20mg and Pariet® (rabeprazole) 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

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$^{grade2\text{-}4\ esophagitis}$

•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

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

The Evidence

(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:

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

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)

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.

Implications to practice
Cost savings

Standard Dose PPIs	Generic omeprazole 20mg Daily	Pariet® rabeprazole 20mg Daily	Pantoloc® pantoprazole 40mg Daily	Prevacid® lansoprazole 30mg Daily	Nexium® esomeprazole 20mg Daily	Losec® omeprazole 20mg Daily
Daily Price$^{\Delta}$	$1.25	$1.30	$1.90	$2.00	$2.10	$2.20
Approximate Monthly Price†	$43.00	$44.40	$61.20	$64.00	$66.80	$69.60

High Dose PPIs	Nexium® 40mg Daily	Generic Omeprazole 40mg Daily	Pariet® 20mg Twice Daily	Pantoloc® 40mg Twice Daily	Prevacid® 30mg Twice Daily	Losec® 20mg Daily
Daily Price$^{\Delta}$	$2.10	$2.50	$2.60	$3.80	$4.00	$4.40
Approximate Monthly Price†	$66.80	$78.00	$80.80	$114.40	$120.00	$131.20

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

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

Alternate prescription pad


Patient:

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
- acidic foods (e.g., tomatoes, lemons)
- alcohol
- overly spicy or high-fat meals
- 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 (eg. 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

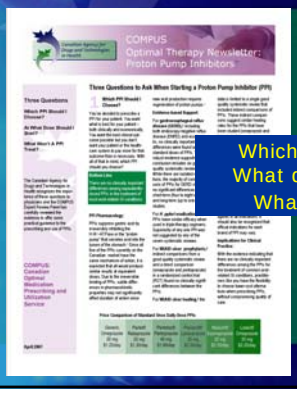
Consult with your **Pharmacist** for the best option for you

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

Doctor Signature: _____

Pharmacist Signature: _____

Optimal therapy newsletter


COMPUS
Optimal Therapy Newsletter: Proton Pump Inhibitors

Three Questions to Ask When Starting a Proton Pump Inhibitor (PPI)

Which PPI should I choose?
What dose should I start At?
What won' t a PPI treat?

Quick reference prescribing aid

Role of pharmacist

- Referral to family physician (Remember Vbad)
- Identify drug related causes
- 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$^{400\text{-}800\text{mcg/day}}$ have similar efficacy in the prevention of NSAID-associated ulcers.

Questions?

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