Physician Presentation

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

Presenter

Title

Affiliation

Date

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Statement of disclosure

Outline

- Objectives
- Background
- Approach to diagnosing Dyspepsia vs. other GI Conditions (including GERD and NSAID-associated PUD)
- Managing GERD, NSAID-associated PUD, and Dyspepsia
- PPIs in Practice – Prescribing Points

Objectives

- Review diagnostic criteria for GERD, Dyspepsia, and Peptic Ulcer Disease (including NSAID-related Upper GI Problems and *H. Pylori*)
- Review the treatment of these conditions, including the role of PPIs
- Review points for prescribing PPIs in practice
  - Efficacy of different PPIs for initial therapy
  - Double dosing in initial therapy
  - Role in asthma, laryngeal symptoms, cough

Background

Canadian Agency for Drugs and Technologies in Health (CADTH)

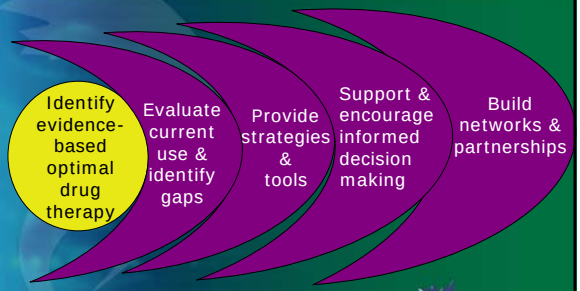
CADTH is an independent, not-for-profit agency funded by Canadian federal, provincial, and territorial governments to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health care decision makers.

CADTH

Stakeholders:

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

What is COMPUS?



Why PPIs?

PPI topic selection criteria included:

- Over- or under-use
- Size of patient population
- Potential impact on health outcomes and cost-effectiveness
- Potential to effect change
- Benefit to multiple jurisdictions
- Measurable outcomes

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

PPI project process

- Identify, summarize and evaluate the clinical evidence in the form of evidence-based statements
- Produce reliable economic evidence
- Understand the current practice in Canada related to PPI prescribing and use
- Identify gaps in practice highlighting areas where current practice differs from the evidence

PPI project process

- Develop key messages regarding the evidence-based statements to address the gaps in practice.
- Select interventions to support the key messages and effect change in the prescribing and use of PPIs
- Develop intervention tools for implementation
- Develop an evaluation framework to measure the effect of the interventions

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 evidence-based optimal drug therapy

- PPI Expert Review Panel reviewed results, voted on statements
- Stakeholder feedback/input (interim reports containing statements and evidence posted on web)
- Published scientific report March 2007
- Develop strategies to support implementation of Optimal Drug Therapy
- Ongoing process to maintain information on 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 (ERP)

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

Conditions related to PPI Project

- Dyspepsia
- GERD
- Peptic Ulcer Disease (PUD)
- *H. Pylori* Infection
- NSAID Associated Ulcer

Dyspepsia

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 or slow digestion or early satiety."

Van Zanten 2000

Uninvestigated Dyspepsia

Endoscopy

Investigated (non-ulcer) Dyspepsia

Uninvestigated Dyspepsia

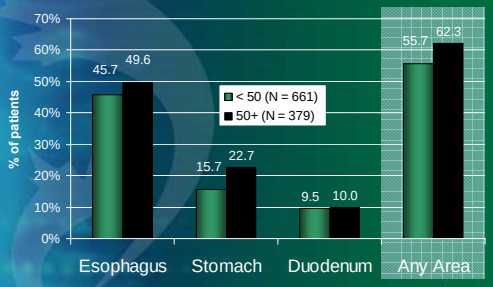
What would the endoscopic findings be if every dyspepsia patient underwent urgent endoscopy?

CADET-PE Study baseline characteristics: N=1040

Age	
< 50	661 (64%)
≥ 50	379 (36%)
Sex	
Male	520 (50%)
Race	
Caucasian	991 (95%)
Hp positive	301 (30%)

Thomson 2003

Prevalence of clinically significant findings by age



Thomson 2003

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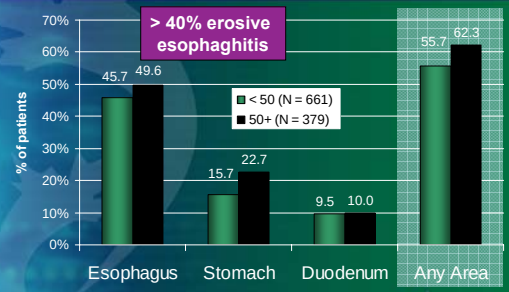
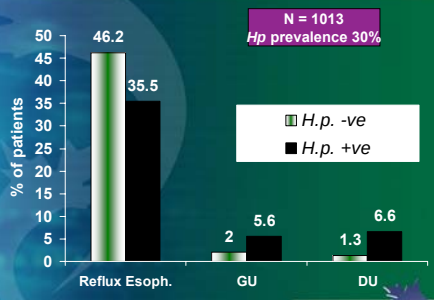


Thomson 2003

Endoscopic findings by *Hp* status



Thomson 2003

What does the CADET-PE study tell us?

Most endoscopic abnormalities are covered by either a course of acid suppressive therapy or anti-Hp treatment.

Thomson 2003

Uninvestigated dyspepsia

- Prompt endoscopy does not produce better outcomes than empirical PPI therapy
- Endoscopy is not warranted in the majority of cases of dyspepsia
- Treatment as uninvestigated dyspepsia

Van Zanten 2000

Five key decision points: 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*?

Van Zanten 2000

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Van Zanten 2000

Are there other possible causes for the symptoms?

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

If YES → treat as appropriate

Van Zanten 2000

Medications associated with dyspepsia

NSAIDS/ASA/COX2 inhibitors

acarbose (Glucobay®)

alcohol

alendronate (Fosamax®)

corticosteroids

metformin (Glucophage®)

antibiotics (erythromycin)

orlistat (Xenical®)

potassium

Theophylline

iron

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

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Van Zanten 2000

Does patient have Alarm symptoms or is patient > 50 yrs?

VBAD

- Vomiting
- Bleeding/anemia
- Abdominal mass/unexplained weight loss
- Dysphagia
- Age > 50

If YES → further investigation is warranted

Van Zanten 2000

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Van Zanten 2000

Is patient using NSAIDs (including ASA)?

If YES:

Stop NSAID therapy (if possible)

If symptoms resolve, but analgesic is still required:

- Avoid NSAID if possible (acetaminophen)
- If NSAID must be used:
  - lowest dose
  - shortest duration
  - consider prophylaxis with standard dose PPI, or misoprostol

Van Zanten 2000

NSAID prophylaxis: should be considered for whom?

- 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

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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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

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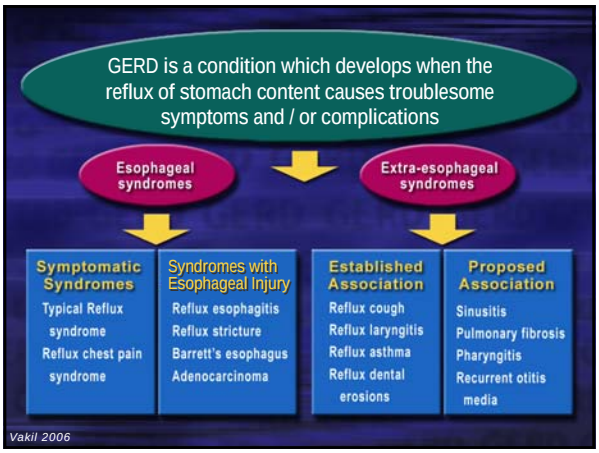
Van Zanten 2000



Vakil 2006

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

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

Uninvestigated GERD:

- dominant symptoms of heartburn and/or regurgitation
- may be associated with other symptoms such as epigastric pain/discomfort
- 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): individuals with GERD who have normal endoscopy results while off treatment.

Armstrong 2005
Vakil 2006
CADTH 2007

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

If YES:

- GERD is the likely diagnosis
- Treat as GERD

GERD treatment

Goals of therapy:

- Resolution of symptoms
- Healing of ulcer or esophagitis, if present
- Prevent long-term sequelae
  - Barrett's esophagus
  - Bleeding
  - Stricture

Heidelbaugh 2003

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:

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

Higher healing rates @ 8 wks

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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

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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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)

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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- 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

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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

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 twice daily 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

GERD Treatment

Initial therapy: 4 – 8 weeks

Following initial therapy:

- 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)

GERD Treatment – Following Initial Therapy

On demand PPI therapy:

- More efficacious than placebo
- More efficacious than continuous standard dose H2RA
- Less efficacious than continuous standard dose PPI

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%
    - On-demand PPI: 45.1%
    - Continuous H2RA: 32.5%

    NNT (95% CI) = 4 (3, 5)

    NNT (95% CI) = 8 (6, 14)
  - Proportion at least 'very satisfied' at 6 months
    - Continuous PPI: 82.2%
    - On-demand PPI: 75.4%
    - Continuous H2RA: 33.5%

    p<0.01

    p<0.0001
  - On-demand patients used 35% less drug on average than continuously-dosed patients

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GERD Treatment

If a patient does not respond following 4-8 weeks of PPI treatment:

- Consider:
  - Switching to another standard dose PPI or increasing to double dose PPI (little evidence to support either strategy)
  - investigation (i.e. endoscopy)
  - alternative diagnosis (symptoms may not be acid related)

Armstrong 2005
Heidelbaugh 2003
Van Zanten 2000

Five Key Decision Points
Univestigated 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)?
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5. Is the patient infected with *H. pylori*?

Van Zanten 2000

Is the patient infected with *H. pylori*?

Non-invasive H. pylori test:

If positive → eradication therapy

Can drug therapy impact Hp testing?

- False negatives are possible
  - Discontinue abx/bismuth 4 weeks prior to testing
  - Discontinue acid suppression 1 week prior

Van Zanten 2000
Hunt 1999
Hunt 1998

H. pylori Eradication Therapy

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 bid + BMT QID
  (bismuth+metronidazole+tetracycline)

Van Zanten 2000

H. pylori eradication – then what?

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

H. pylori eradication – then what?

Is follow-up testing to confirm eradication required?

- Not generally recommended *unless* patient remains symptomatic

What if the eradication therapy fails?

- Try a different first-line therapy than the initial therapy tried

Van Zanten 2000
Hunt 1999
Hunt 1998

Five Key Decision Points
Univestigated Dyspepsia

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

If NO → Dyspepsia is the likely diagnosis

Van Zanten 2000

Dyspepsia Treatment

Non-medical treatment options:

- Avoid foods that worsen symptoms
- Avoid lying down 2-3 hours after eating
- Avoid tight-fitting clothing
- Stop smoking (or reduce smoking)
- Elevate the head of the bed using blocks
- Eat smaller meals and chew food well
- Lose weight, if appropriate
- Review medications used
- Reduce stress

Thomson 2002
Kaltenbach 2006
Heidelbaugh 2003

Dyspepsia Treatment

Over-the-counter (OTC) Medications:

Antacids

- 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
- Consider concurrent clinical conditions & convenience

Thomson 2002

Dypepsia Treatment

Over-the-counter (OTC) Medications (con't)

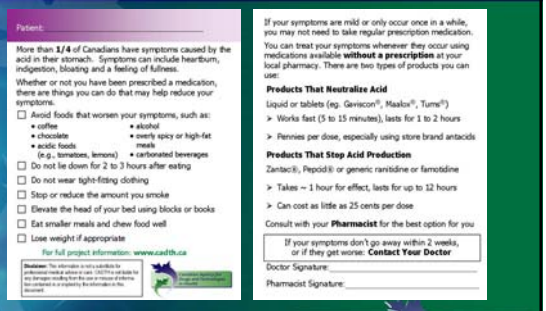
***H2RAs* - Symptom relief similar to antacids, but takes 1 hour for effect**

- duration of effect is longer
- Famitodine (Pepcid®) 10mg- ranitidine (Zantac®) 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 a OTC product for occasional symptoms related to dietary indiscretion

Thomson 2002

Alternate Prescription Pad



Dyspepsia Treatment

PPIs or H2RAs?

Initial standard-dose PPI therapy is more efficacious than standard-dose H2RAs at reducing symptoms in patients with dyspepsia (H. pylori negative, uninvestigated)

Uninvestigated dyspepsia

1 RCT N=512

- *Included: pts with epigastric pain, with or without heartburn and/or regurgitation*
- *Excluded: pts. with heartburn/regurg but no epigastric pain or GERD diagnosis*

Success rate (no or minimal symptoms) @ 4 weeks

- Omeprazole 51% (95% CI: 43%-55%)
- Ranitidine 36% (95% CI: 28%-44%), p=0.01 vs. PPI
- Placebo 23% (95% CI: 16%-31%)
- NNT =7 (95% CI: 4-29) PPI vs H2RA

Complete symptom relief (Global overall severity score =1)

- Omeprazole 24% (95% CI: 17%-31%)
- Ranitidine 11% (95% CI: 6%-16%), p=0.005 vs. PPI
- Placebo 4% (95% CI: 0.5%-7%)
- NNT 8 (95% CI: 5-25) PPI vs H2RA

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)

PPIs in Practice: Prescribing Points

- **Choosing a PPI for initial therapy**
- **Double-dosing in initial therapy**
- **Asthma, cough, laryngeal symptoms**

Choosing a PPI for Initial Therapy

All PPIs are equally efficacious in the initial treatment of GERD and other common GI conditions

There are no clinically important differences between the PPIs at standard doses for:

- *H. pylori* eradication
- GERD, ENRD, esophagitis
- NSAID-associated ulcer prophylaxis and healing

The Evidence

GERD / ENRD / Esophagitis

- *Six good quality systematic reviews showed no clinically important differences in standard-dose PPIs as initial therapy*
- *Isolated exceptions, majority showed no differences*
- *Comparisons showing some degree of difference involved non-equivalent comparisons (e.g. high dose vs. standard dose)*

Edwards 2001 McDonagh 2005
Vakil 2003 Gisbert 2004
Wang 2005 Gisbert 2004
McQuaid 2005 Gisbert 2003
Donnellan 2004 Vergara 2003

The Evidence

H. pylori Eradication

Seven systematic reviews (5 of good quality) showed PPIs have similar efficacy when used in triple therapy regimens

Edwards 2001 *McDonagh 2005*
Vakil 2003 *Gisbert 2004*
Wang 2005 *Gisbert 2004*
McQuaid 2005 *Gisbert 2003*
Donnellan 2004 *Vergara 2003*

The Evidence

NSAID Ulcer Prophylaxis

- *Good quality systematic review of 7 RCTs (indirect comparison):*
  - Different PPIs reduced ulcer risk to a similar degree
- *One RCT directly compared omeprazole vs pantoprazole and found no difference in ulcer risk*

NSAID Ulcer Healing

- *Good quality systematic review of 3 RCTs (indirect comparison):*
  - Similar healing rates for the PPIs that have been studied (omeprazole & lansoprazole)

McDonagh 2005
Regula 2006

The Evidence – Limitations

- *Isolated studies may show differences in efficacy – must be balanced against the weight of the evidence*
- ***Caution:** non-equivalent dose comparisons*
- *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*
- *Balance evidence with individual patient needs*

Practice implications

Prescribing may be optimized by focusing on lower cost PPIs

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[4]	$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

CADTH 2007

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

Potential Cost-savings to Patients

- *Generic omeprazole 20 mg and Pariet (rabeprazole) 20 mg are the least expensive standard-dose PPIs in Canada*
- *Prescribing a PPI that cost $1.40/day vs. $2.20/day could save almost **$300.00 per year** in drug costs.*

Double vs. Standard Dosing

Doubling the standard daily-doses of PPIs, as initial therapy, is no better than standard daily-dose therapy (in erosive esophagitis)

Double-Dose PPIs – Gaps in Research:

- Uninvestigated GERD with severe symptoms?
- Symptomatic GERD, ENRD, erosive esophagitis despite standard-dose PPI therapy?

CADTH 2007

The Evidence

High or Double-dose PPIs: initial Rx Erosive Esophagitis

- 6 RCTs[N=1388]: 2 RCTs very good, 1 good quality, 3 poor quality
- 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 small but statistically significant benefit: Clinical importance unclear

CADTH 2007
McDonagh 2005

The Evidence

Double-dose initial Rx NSAID-induced ulcer

- 2 RCT [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)

CADTH 2007

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)

Yeomans 1998

PPIs and Asthma,Chronic Cough, and Laryngeal Symptoms

*PPIs are **not efficacious** in treating cough, asthma or laryngeal symptoms that may be associated with GERD*

CADTH 2007

The Evidence

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

CADTH 2007

The Evidence

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)

The Evidence

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

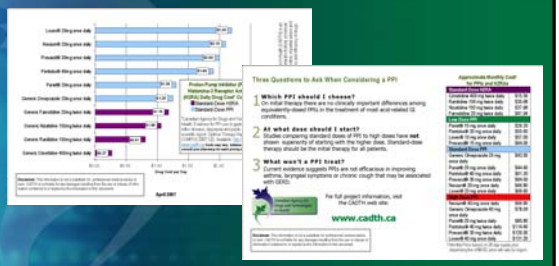
Limitations:

- Small pooled sample size: analysis likely underpowered
- Heterogeneity in study population

PPIs in Practice: Prescribing Points

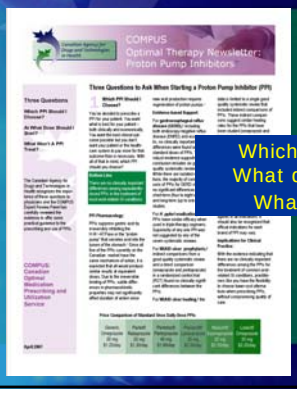
- There are no clinically important differences among equivalently dosed PPIs in the initial treatment of most acid-related GI conditions
- Studies comparing standard doses of PPI to high doses have **not** shown superiority of starting with the higher dose. Standard-dose therapy should be the initial therapy for most patients
- Current evidence would suggest PPIs are not efficacious in improving asthma, laryngeal symptoms or chronic cough that may be associated with GERD

Quick reference prescribing aid



Alternate prescription pad

Optimal therapy newsletter



PPI Intervention 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

Pharmacist Materials:
- Interactive and Didactic Presentation

Patient Education Materials:
- Information Brochure / Alternate Prescription Pad

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Questions?

References

1. *Canadian Agency for Drugs and Technologies in Health. Evidence for PPI use in gastroesophageal reflux disease, dyspepsia and peptic ulcer disease: scientific report.* Optimal Therapy Report - COMPUS *2007;1(2). Available:* http://www.cadth.ca/index.php/en/compus/current-topics/ppis *(accessed 2007 Mar 28).*
2. *Armstrong D, Marshall JK, Chiba N, Enns R, Fallone CA, Fass R, et al. Canadian consensus conference on the management of gastroesophageal reflux disease in adults: update 2004.* Can J Gastroenterol *2005;19(1):15-35.*
3. *Bazaldua OV, Schneider FD. Evaluation and management of dyspepsia.* Am Fam Physician *1999;60(6):1773-8. Available:* http://www.aafp.org/afp/991015ap/1773.html *(accessed 2005 Jul 18).*
4. *Berger ML, Bingefors K, Hedblom EC, Pashos CL, Torrance GW, editors.* Health care cost, quality, and outcomes: ISPOR book of terms. *Lawrenceville: International Society for Pharmacoeconomics and Outcomes Research; 2003.*

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References

5. *Donnellan C, Sharma N, Preston C, Moayyedi P. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease [Cochrane review].* In: Cochrane Database of Systematic Reviews 2004 Issue 4. *Chichester (UK): John Wiley & Sons, Ltd; 2004. DOI: 10.1002/14651858.CD003245.pub2.*
6. *Edwards SJ, Lind T, Lundell L. Systematic review of proton pump inhibitors for the acute treatment of reflux oesophagitis.* Aliment Pharmacol Ther *2001;15(11):1729-36.*
7. *Gisbert JP, Khorrami S, Calvet X, Pajares JM. Systematic review: rabeprazole-based therapies in Helicobacter pylori eradication.* Aliment Pharmacol Ther *2003;17(6):751-64.*
8. *Gisbert JP, Pajares JM. Esomeprazole-based therapy in Helicobacter pylori eradication: a meta-analysis.* Dig Liver Dis *2004;36(4):253-9.*
9. *Gisbert JP, Khorrami S, Calvet X, Pajares JM. Pantoprazole based therapies in Helicobacter pylori eradication: a systematic review and meta-analysis.* Eur J Gastroenterol Hepatol *2004;16(1):89-99.*
10. *Gisbert JP, Pajares JM. Systematic review and meta-analysis: is 1-week proton pump inhibitor-based triple therapy sufficient to heal peptic ulcer?* Aliment Pharmacol Ther *2005;21(7):795-804.*

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References

11. *Heidelbaugh JJ, Nostrant TT, Kim C, Van Harrison R. Management of gastroesophageal reflux disease.* Am Fam Physician *2003;68(7):1311-8.*
12. *Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard.* Med Decis Making *2000;20(3):332-42.*
13. *Hunt R, Thomson AB. Canadian Helicobacter pylori consensus conference. Canadian Association of Gastroenterology.* Can J Gastroenterol *1998;12(1):31-41.*
14. *Hunt RH, Fallone CA, Thomson AB. Canadian Helicobacter pylori consensus conference update: infections in adults. Canadian Helicobacter Study Group.* Can J Gastroenterol *1999;13(3):213-7.*
15. *Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach.* Arch Intern Med *2006;166(9):965-71.*
16. *Lanza FL. A guideline for the treatment and prevention of NSAID-induced ulcers. Members of the Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology.* Am J Gastroenterol *1998;93(11):2037-46.*

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References

17. *McDonagh MS, Carson S.* Drug class review on proton pump inhibitors: final report update 3. *Portland (OR): Oregon Health & Science University; 2005.*
18. *McQuaid KR, Laine L. Early heartburn relief with proton pump inhibitors: a systematic review and meta-analysis of clinical trials.* Clin Gastroenterol Hepatol *2005;3(6):553-63.*
19. *Regula J, Butruk E, Dekkers CP, de Boer SY, Raps D, Simon L, et al. Prevention of NSAID-associated gastrointestinal lesions: a comparison study pantoprazole versus omeprazole.* Am J Gastroenterol *2006;101(8):1747-55.*
20. *Thomson AB, Barkun AN, Armstrong D, Chiba N, White RJ, Daniels S, et al. The prevalence of clinically significant endoscopic findings in primary care patients with uninvestigated dyspepsia: the Canadian Adult Dyspepsia Empiric Treatment - Prompt Endoscopy (CADET-PE) study.* Aliment Pharmacol Ther *2003;17(12):1481-91.*

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References

21. *Thomson P. Dyspepsia and GERD. In:* Patient self-care: helping patients make therapeutic choices. *1st ed. Ottawa: Canadian Pharmacists Association; 2002. p.256-63.*

22. *Tytgat GN. Treatment of peptic ulcer.* Digestion *1998;59(5):446-52.*

23. *Vakil N, Fennerty MB. Direct comparative trials of the efficacy of proton pump inhibitors in the management of gastro-oesophageal reflux disease and peptic ulcer disease.* Aliment Pharmacol Ther *2003;18(6):559-68.*

24. *Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus.* Am J Gastroenterol *2006;101(8):1900-20.*

25. *Van Zanten SJO, Sherman PM, Hunt RH, . Helicobacter pylori: new developments and treatments.* CMAJ *1997;156(11):1565-74. Available: http://www.cmaj.ca/cgi/reprint/156/11/1565 (accessed 2006 Feb 3).*

References

26. *Van Zanten VSJ, Flook N, Chiba N, Armstrong D, Barkun A, Bradette M, et al. An evidence-based approach to the management of uninvestigated dyspepsia in the era of Helicobacter pylori.* CMAJ *2000;162(12 Suppl):S3-S23. Available: http://www.cmaj.ca/cgi/content/full/162/12_suppl/s3 (accessed 2007 Apr 9).*

27. *Vergara M, Vallve M, Gisbert JP, Calvet X. Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for Helicobacter pylori eradication.* Aliment Pharmacol Ther *2003;18(6):647-54.*

28. *Wang W, Huang J, Zheng G, Xia HHX, Wong W, Lam S, et al. Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: a meta-analysis.* World J Gastroenterol *2005;11(26):4067-77. Available: http://www.wjgnet.com/1007-9327/abstract_en.asp?f=4067&v=11 (accessed 2006 Nov 28).*