This Executive Summary is based on a comprehensive Scientific Report (Optimal Therapy Report – COMPUS: Evidence for PPI use in gastroesophageal reflux disease, dyspepsia and peptic ulcer disease [Scientific Report]) and economic report on the topic, prepared by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS), a service of the Canadian Agency for Drugs and Technologies in Health (CADTH).

This report is a comprehensive review of the existing public literature available to CADTH at the time it was prepared and it was guided by expert input and advice throughout its preparation. The conclusions [statements] were provided by experts. The authors have also considered input from other stakeholders.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgement in respect of the care of a particular patient or other professional judgement in any decision making process nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this Report.

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Production of this report is made possible through a financial contribution from Health Canada.

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ABBREVIATIONS

b.i.d.  twice daily  
CAC     COMPUS Advisory Committee  
CADET   Canadian Adult Dyspepsia Empirical Treatment  
CDTI    Canadian Disease and Therapeutic Index  
CEP     Centre for Effective Practice  
COMPUS  Canadian Optimal Medication Prescribing and Utilization Service  
DUR     Drug Utilization Review  
EE      erosive esophagitis  
ENRD    endoscopic-negative reflux disease  
ERP     Expert Review Panel  
GERD    gastroesophageal reflux disease  
GI      gastrointestinal  
H2RA    histamine-2 receptor antagonist  
H. pylori  Helicobacter pylori  
IMS     IMS Health  
ICD     International Classification of Disease  
NSAID   non-steroidal anti-inflammatory drug  
OA      osteoarthritis  
q.d.    once daily  
PAC     PPI plus amoxicillin and clarithromycin  
PPI     proton pump inhibitor  
PUD     peptic ulcer disease  
QALY    quality-adjusted life-year  
QOL     quality of life  
qu.i.d.  four times daily  
RA      rheumatoid arthritis  
RCT     randomized control trial  
SR      systematic review  
UD      uninvestigated dyspepsia  
UG      uninvestigated GERD
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Background

The goal of the Canadian Agency for Drugs and Technologies in Health (CADTH), through its COMPUS program, is to identify and promote optimal drug prescribing and use. Strategies, tools, and services are provided to encourage the use of evidence-based clinical and cost-effectiveness information in decision making among health care providers, consumers and policy makers.

Proton pump inhibitors (PPIs) are a class of medications commonly prescribed and widely used in Canada. Between 2003 and 2004, PPI prescriptions dispensed increased by 15%, from 10.8 million to 12.4 million. However questions exist about whether PPIs are being prescribed and used appropriately. Both over- and under-usage of PPIs have been reported, and costs associated with inappropriate prescribing and use may be considerable. As a result, COMPUS was directed by federal, provincial and territorial governments to focus on the optimal use of PPIs in Canada.

To achieve this goal, a multi-step process was undertaken by COMPUS that started with the identification and examination of the evidence and culminated in the development of intervention tools to be implemented, with the intent of optimizing PPI prescribing and use behaviour and ultimately improving health outcomes. This process was guided by the COMPUS Advisory Committee (CAC) with representatives from the federal, provincial and territorial Health Ministries and related health organizations, and by the Expert Review Panel (ERP) – a panel of clinical and research experts (gastroenterologists, family physicians, pharmacists and researchers).

The PPI Project process consisted of the following steps:

- 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
- develop key messages based on gaps in practice and the evidence-based statements
- 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.

This report summarizes each step of the process. A series of Optimal Therapy Reports on PPIs provides further information on each of the steps of the PPI Project process and includes:

- evidence-based clinical statements (complete scientific report)
- evidence-based cost-effectiveness statements (with the results of the economic analysis coming available at a later date)
Proton Pump Inhibitor project Overview: Summaries

2 Research Focus

The use of PPIs was specifically addressed for the management of:
• gastroesophageal reflux disease (GERD)
• dyspepsia
• peptic ulcer disease (PUD)
• H. pylori infection
• non-steroidal anti-inflammatory drug-associated ulcer.

The COMPUS Advisory Committee (CAC), which includes representatives from the federal, provincial, and territorial Health Ministries, and related health organizations requested a number of areas of focus including:
• double daily dose therapy with PPIs versus standard daily dose PPI
• long-term/chronic use of PPIs – the role of on-demand, intermittent and regular daily dose PPIs
• the appropriateness of step-up therapy (e.g., from H2RAs to PPIs or from regular dose PPIs to double-dose PPIs, or from low-dose PPIs to regular dose PPIs)
• the appropriateness of step-down therapy [e.g., from double-dose PPIs to standard dose PPIs, from standard dose PPIs to low-dose PPIs, or from PPI maintenance to histamine-2 receptor antagonists (H2RA) therapy]
• the relative clinical equivalence of PPIs
• evidence for the use of PPIs in managing dyspepsia
• the role of PPIs for preventing gastrointestinal complications in non-selective NSAID users.

3 PPI Clinical Analysis

The primary objective of the clinical component of this project was to develop evidence-based statements that specifically addressed the use of PPIs for the management of:
• gastroesophageal reflux disease (GERD)
• dyspepsia
• peptic ulcer disease (PUD)
• H. pylori infection
• non-steroidal anti-inflammatory drug-associated ulcer.

In addition, research gaps where evidence was insufficient or lacking were identified, pointing the direction for future research.
4 PPI Economic Analysis

The objective of the economic component of this project was to compare expected costs and outcomes of various primary care strategies for the management of patients with:

- moderate-to-severe heartburn predominant GERD Symptoms
- uninvestigated non-heartburn predominant dyspepsia (UD)
- prevention of GI complications in patients with musculoskeletal conditions (primarily RA and OA) who require non-steroidal anti-inflammatory drug (NSAID) therapy for more than three weeks.

5 Methods

5.1 Clinical

Systematic reviews and randomized controlled trials related to the efficacy of PPIs for various gastrointestinal conditions were identified from guidelines and consensus documents, and a literature search. Evidence-based statements regarding the efficacy of PPIs were formulated based on the evidence. An Expert Review Panel (ERP) reviewed the statements and the corresponding evidence, and voted on the degree of acceptance for each statement. Areas without sufficient evidence were identified as Research Gaps.

5.2 Economic

The economic studies were built upon previously published models. In collaboration with the ERP on PPIs, modifications were made in order to update the original models. Model structure and process, resource utilization costs, resource allocations, outcome variables, and transition probabilities were verified and validated by members of the COMPUS ERP. Analyses covered a one-year period, and were from a third-party payer perspective. Sensitivity analyses were conducted to determine the robustness of the results of each model.

a) Moderate-to-severe heartburn predominant GERD symptoms

Five strategies were compared – two on-demand approaches (standard dose H2RA or standard dose PPI for up to four weeks until resolution of symptoms, with no further treatment until a recurrence of symptoms), two maintenance approaches (acute treatment for four weeks with a standard dose of H2RA followed by continuous maintenance treatment, with a H2RA at the same dose; or standard dose PPI followed by continuous maintenance treatment, with a PPI at the same dose to prevent recurrences); and one step-down maintenance approach (acute treatment with a standard dose PPI for four weeks, followed by continuous maintenance treatment, with a H2RA to prevent recurrences). Separate analyses were conducted for erosive esophagitis (EE), endoscopic- negative reflux disease (ENRD), and uninvestigated GERD (UG) patients.

b) Uninvestigated non-heartburn predominant dyspepsia (UD)

Six strategies were compared – two test and treat approaches (triple therapy – PPI, clarithromycin and amoxicillin – and omeprazole or triple therapy and ranitidine) in the treatment of UD patients, with four other approaches: empirical antisecretory therapy in all
patients (omeprazole or ranitidine), and prompt upper gastrointestinal endoscopy of all patients (with PPI or H2RA-based acid suppression).

c) **Prevention of GI complications in patients with musculoskeletal conditions (primarily RA and OA) who require NSAID therapy for more than three weeks**

Five NSAID prophylaxis strategies were compared – H2RAs (ranitidine 300 mg b.i.d.), PPIs (omeprazole 20 mg q.d.), misoprostol 200 μg q.i.d., or placebo all in combination with a non-specific NSAID (diclofenac 50 mg b.i.d.), or a COX-selective anti-inflammatory agent (celecoxib 200 mg b.i.d.).

Stakeholder feedback on these three economic studies is currently under review. The results of the economic analysis will be available at a later date.

6 **Results**

Following are the main conclusions from the clinical analysis produced by COMPUS. All results are available online at www.cadth.ca.

6.1 **Gastroesophageal Reflux Disease (GERD)**

**Clinical Evidence-based Statements**

a) **Uninvestigated GERD**

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

• Symptom relief rates ranged from 55% to 75% with PPIs versus 27% to 58% with H2RAs at four to eight weeks. The panel recognized that quality of life (QOL) is an important issue, but there was uncertainty as to which outcomes and measures of QOL are of importance.

Approximately 20% of patients with uninvestigated GERD will remain asymptomatic off therapy for up to six months after a successful course of initial therapy (for four to eight weeks) with a PPI or H2RA.

• The majority of patients had relapsed six months after treatment discontinuation with a median time to relapse of only eight to nine days.

For patients with uninvestigated GERD who respond to initial PPI therapy:

• continued PPI therapy is more efficacious than step-down to H2RAs for providing symptom relief
• subsequent on-demand PPI therapy is more efficacious than continuous standard-dose H2RAs
• subsequent on-demand PPI therapy is less efficacious than continuous standard regular dose PPI therapy for heartburn resolution.

• The evidence for these statements is very limited, the severity of symptoms at baseline may be important for the degree of success with step-down therapy, and a significant proportion of patients did well with on-demand therapy.
b) **Endoscopic Negative Reflux Disease (ENRD)**

PPIs are more efficacious than H2RAs, as initial therapy, for improvement of heartburn symptoms at four weeks in patients with ENRD.

- The proportion achieving heartburn relief was 53% versus 42% in the comparison of standard-dose PPIs versus H2RAs, and 50% versus 44% in the comparison of half-dose PPIs versus H2RAs.

PPIs are no more efficacious than H2RAs for improving quality of life in patients with ENRD.

- The assembled evidence does not show any improvement on general QOL scores, and there were conflicting opinions in both the literature, and among Panel members, on the appropriateness of using certain scales to measure symptoms.

c) **Erosive Esophagitis**

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

- In the short-term studies, symptomatic response rates to H2RAs ranged from approximately 22% to 52%, while those of PPIs ranged from 46% to 78%. Regarding healing rates in short-term studies, 56% to 90% of PPI-treated subjects experienced healing of esophagitis, as compared to 26% to 76% with H2RAs. The systematic review (SR) on long-term therapy reported healing in 82% of those given standard-dose PPI versus 52% with standard-dose H2RA at six months.

Doubling the standard daily doses of PPIs, as initial therapy, is no better than standard daily dose PPI therapy for healing erosive esophagitis.

- The Panel expressed some reservation regarding the relatively small number of randomized control trials (RCTs) that specifically addressed esophagitis of Grades 2 to 4, and the ‘poor’ quality ratings of these trials.

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.
  - A large proportion of patients experience relapse of esophagitis on both half-dose PPIs (39%) and H2RAs (66%).
- Half-dose PPIs are less efficacious than standard-dose PPIs as maintenance treatment for the prevention of symptomatic and endoscopic relapse.
  - The actual difference is small (e.g., patients with significant symptoms at six to 12 months were 31% with half-dose and 36% with standard-dose PPIs in one SR) and may be of limited clinical significance.
- Subsequent on-demand PPI therapy is less efficacious than continuous standard-dose PPI therapy.
  - The proportion with symptomatic relapse at six months was similar for on-demand and continuous PPI, as was patient satisfaction. There are no studies assessing the effect of on-demand therapy in terms of long-term complications of erosive esophagitis.

PPIs are not efficacious in improving:

- asthma in patients with concomitant GERD
• although 12 RCTs were included in the SR, the total sample size was relatively small
• laryngeal symptoms (i.e., cough, throat clearing, globus, hoarseness, sore throat) associated with reflux
  o there is limited evidence for this Statement, the validity of some outcomes was uncertain, study populations differed across studies, results were sometimes contradictory, and subjects were enrolled based on laryngopharyngeal signs and symptoms; only about 15% to 50% of subjects had reflux as measured by 24-hour pH-metry; in the absence of GERD symptoms, there is no evidence that PPIs are useful
• chronic cough with or without GERD
  o the evidence for this Statement is limited to trials with small sample sizes that were likely underpowered, and enrolled study populations exhibited significant heterogeneity.

There are no clinically important differences among standard-doses of PPIs (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, rabeprazole 20 mg, esomeprazole 20 mg) in the treatment of symptomatic GERD, ENRD and esophagitis.
• The esomeprazole Product Monograph recommends 20 mg daily as the initial dose for all indications, with the exception of erosive esophagitis and \emph{H. pylori} eradication; the Panel recognized that the Canadian Association of Gastroenterology defines the standard-dose of esomeprazole as 40 mg/day.

PPIs have a similar adverse event rate (generally minor) to \emph{H}2\emph{R}As in GERD randomized controlled trials of up to one year duration.
• The Panel recognizes that safety information derived from RCTs has significant limitations, and post-marketing surveillance data were not considered for this Statement. Observational studies have linked PPI use with \emph{C. difficile} infection, and associations between PPI use, and pneumonia and hip fractures, have also been reported.

6.2 Dyspepsia

Clinical Evidence-based Statements

\textbf{a) Uninvestigated Dyspepsia}

Initial (up to four weeks) standard-dose PPI therapy is more efficacious than standard-dose \emph{H}2\emph{R}As at reducing symptoms in patients with \emph{H. pylori}-negative, otherwise uninvestigated dyspepsia.
• Among patients with no or minimal heartburn or regurgitation enrolled in the Canadian Adult Dyspepsia Empirical Treatment-\emph{H. pylori}negative (CADET-HN) trial, 48.7% achieved symptom relief at four weeks with standard dose PPI, versus 39.5% with standard dose \emph{H}2\emph{R}A.

Management strategy based on initial (prompt) endoscopy does not produce better outcomes (e.g., improvement of symptoms, failure of treatment strategy, quality of life) than empirical PPI therapy in patients with uninvestigated dyspepsia.
The only available evidence was a small RCT of poor quality conducted in referral patients. The ERP considered it unlikely that prompt (i.e., immediate) endoscopy would be a practical strategy for initial management of dyspepsia in Canada.

For the maintenance treatment of dyspepsia symptoms in *H. pylori*-negative patients with uninvestigated dyspepsia:
- On-demand PPI therapy is more efficacious than on-demand placebo.
- On-demand PPI therapy is not more efficacious than on-demand H2RA therapy.
  - In the CADET-HN trial, on-demand omeprazole 20 mg was significantly more efficacious than on-demand placebo, only in the subset of patients who responded to initial four-week therapy with omeprazole 20 mg daily.

**b) Functional Dyspepsia**

For the improvement of symptoms in functional dyspepsia:
- standard-dose PPIs for four to eight weeks are more efficacious than placebo
- standard-dose PPIs are not more efficacious than H2RAs
  - standard dose PPIs were not consistently superior to placebo across all studies in patients with non-heartburn predominant functional dyspepsia.

### 6.3 Peptic Ulcer Disease

**Clinical Evidence-based Statements**

**a) *H. pylori* Eradication**

All PPIs have similar efficacy in triple therapy regimens for *H. pylori* eradication.
- Most trials compared standard doses of PPIs administered twice daily.

Continued treatment with PPI after a course of *H. pylori* eradication therapy does not produce higher ulcer healing rates than eradication therapy alone in *H. pylori*-infected patients with uncomplicated duodenal ulcer.
- This Statement does not apply to gastric ulcers or bleeding ulcers.

**b) NSAID-associated Ulcer**

Standard-dose PPI therapy for four to eight weeks produces higher healing rates of NSAID-associated ulcers than H2RAs or misoprostol 800 μg/day, when NSAIDs are continued.
- All studies assessed healing of endoscopic ulcers; however, the relevance of this to more clinically important outcomes, such as healing of symptomatic or complicated ulcers, is uncertain.

Different PPIs produce similar healing rates of NSAID-associated ulcers.
- No studies directly comparing different PPIs were identified; however, based on indirect comparisons, there were no apparent differences in healing efficacy between PPIs.

For the secondary prevention of NSAID-associated endoscopic gastric and duodenal ulcers:
- standard-dose PPIs are more efficacious than standard-dose H2RAs
• standard-dose PPIs are similar in efficacy to misoprostol 400 800 μg/day.
  o Studies directly comparing standard dose PPI versus double dose H2RAs in preventing NSAID-associated ulcers are lacking.
  o As all studies focused on the prevention of endoscopic ulcers, the generalizability to ulcer complications is limited. The data supporting PPIs for the prevention of ulcer complications is poor.

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

• All studies included patients who were H. pylori-negative or had the infection successfully eradicated.
• Only two NSAIDs (i.e., diclofenac and naproxen) were studied in the identified trials.

Different PPIs reduce ulcer risk to a similar degree when given to NSAID users for ulcer prophylaxis.
• Only one study directly comparing one PPI with another was identified. In this trial, there was no difference in NSAID-ulcer relapse between standard doses of omeprazole and pantoprazole. Based on indirect comparisons in other studies, there were also no apparent differences between other PPIs.

7 Research Gaps

Our clinical and economic analyses revealed a number of areas where data was lacking or insufficient to provide clear direction. These gaps represent possible future research questions (listed herein) to be addressed.

a) Gaps Due to a Lack of Data

GERD
• Is there a role for half-dose or double-dose PPIs for the initial management of uninvestigated GERD?
• Is continued PPI therapy more efficacious than stepping down to H2RAs, in patients with ENRD who have completed their initial course of PPIs?
• If a patient with uninvestigated GERD, erosive esophagitis or ENRD remains symptomatic after an adequate course of regular dose PPIs, will doubling the dose of PPIs improve the outcome?
• How should PPIs be optimally used in patients with Barrett’s esophagus?
• What is the optimal duration of PPI therapy for patients with erosive esophagitis complicated by strictures?

Dyspepsia
• Is standard-dose PPI therapy more efficacious than antacids, alginites or standard-dose H2RAs at reducing dyspeptic symptoms in patients with uninvestigated dyspepsia?
• Is continuous maintenance therapy with standard-dose PPIs more efficacious than continuous maintenance therapy with H2RAs in uninvestigated dyspepsia?
PUD
- In patients with uncomplicated gastric ulcers, will continued treatment with a PPI after a course of H. pylori eradication therapy produce higher ulcer healing rates than eradication therapy alone in H. pylori-infected patients?
- Is 10 days of H. pylori eradication therapy with triple therapy (PAC and PMC) as efficacious as 14 days?

b) Gaps With Data, but no Clear Answer

GERD
- Is on-demand PPI therapy less efficacious than continuous standard-dose PPI therapy for patients with ENRD who respond to initial PPI therapy?
  - The outcomes studied in the available trials were generally subjective, and the differences between on-demand and continuous therapy for QOL and satisfaction were usually small, with the evidence often contradictory. On-demand therapy may be preferred by some patients.
- Is surgical anti-reflux therapy more efficacious than maintenance PPI therapy (when dose adjustment based on symptoms is allowed), in patients with erosive esophagitis?
  - Limitations of the evidence include lack of blinding and patient selection, lack of reporting of p-values for some outcomes, clinical relevance and validity of outcomes, and difficulty in interpretation of outcomes. Variations in techniques and expertise among studies may be important confounders. Long-term follow-up data is needed to measure outcomes after laparoscopic surgery.

Dyspepsia
- Is test and treat for H. pylori infection as efficacious as empirical PPI therapy, as an initial therapeutic strategy for the treatment of uninvestigated dyspepsia (H. pylori status unknown)?
  - Panel members noted that the rate of H. pylori infection in the available evidence was higher than the overall prevalence of H. pylori infection in Canada.

For complete details on all the clinical and economic results, please refer to the COMPUS Optimal Therapy Reports.

8 Current Practice

With the available evidence revealing the optimal prescribing and use of PPIs, the Current Practice Analysis was necessary to foster an understanding of how PPIs are currently being prescribed and used in Canada. It was critical to have a clear picture of the current practice in Canada regarding PPIs so that gaps between the current practice and the optimal prescribing and use could be identified and addressed.

The current practice in the prescribing and use of PPIs was determined from trends identified by COMPUS, in collaboration with the Centre for Effective Practice (to identify practice issues) and IMS Health Consulting Inc. (for PPI utilization data).
The Centre for Effective Practice (CEP) is a not-for-profit unit of the Department of Family and Community Medicine at the University of Toronto. The primary objective of the CEP’s involvement was to describe the current practice in physicians’ and pharmacists’ use of PPIs to manage uninvestigated gastroesophageal reflux disease (GERD), uninvestigated dyspepsia and NSAID-induced peptic ulcer disease (PUD). To achieve their objective, CEP invited participants to complete an online survey that focused on the use of PPIs to manage specific gastrointestinal problems from a primary care perspective.

The Physician Survey posed a range of questions including:
- background questions
- general questions about PPI prescribing for a range of GI conditions
- clinical case scenarios
- barriers to the optimal management of GI conditions.

IMS Health Consulting Inc. used their Canadian Disease and Therapeutic Index (CDTI) database to generate a report on estimated utilization of PPIs as initial therapy for the management of GERD and dyspepsia.

The CDTI database consists of records of patient visits and prescribed treatments by diagnosis. Data are collected from a panel of physicians that record the detail of every transaction completed during a set data collection period. Data derived from a sample of 289 physicians are used for identifying the relative proportions of medications being prescribed by diagnosis. The data include only office-based physicians, and the data analysis was conducted for 2005 and 2006. The diagnoses targeted by IMS in this report were uninvestigated GERD and uninvestigated dyspepsia.

For more information about the results of the current practice analysis, please refer to the Optimal Therapy Report – COMPUS: Current Practice Analysis Report for the Prescribing and Use of Proton Pump Inhibitors.2

9 Gaps in Practice

The elucidation of the evidence for the optimal prescribing and use of PPIs, together with the current practice information detailing how PPIs are currently prescribed and used, allowed for a gap analysis to be performed. In this analysis, practice gaps between the evidence and the current prescribing and use of PPIs were identified. In addition, focus groups to further explore the identified gaps with physicians and pharmacists were conducted in collaboration with the Department of Family and Community Medicine’s Centre for Effective Practice (CEP) at the University of Toronto.3

a) Gap #1

Although there is no clinically important difference in efficacy amongst the PPIs for the initial management of various gastrointestinal conditions, physicians are preferentially prescribing different PPIs based on indication.

Available evidence indicates that PPIs are equally efficacious as initial therapy for various gastrointestinal conditions. Evidence-based statements from the Scientific Report1 supporting this identified gap include:
• There are no clinically important differences among standard doses of PPIs (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, rabeprazole 20 mg, esomeprazole 20 mg) in the treatment of symptomatic GERD, ENRD and esophagitis.
• All PPIs have similar efficacy in triple therapy regimens for H. pylori eradication.
• Different PPIs produce similar healing rates of NSAID-associated ulcer.
• Different PPIs reduce ulcer risk to a similar degree when given to NSAID users for ulcer prophylaxis.

However, the current practice analysis indicates that physicians are preferentially prescribing different PPIs based on indication and are not choosing the most cost-effective PPI options when initiating therapy.

When discussing this gap, physician and pharmacist focus group participants identified three possible reasons as to why a physician may choose one PPI over another:
• health insurance coverage
• the unique needs of each individual patient
• pharmaceutical industry samples, industry-sponsored information.

Participants identified four major reasons as to why physicians might not choose the most cost-effective option when initiating PPI therapy:
• the pharmaceutical industry (sponsored dinners, product launches, samples, information – all reported by participants to be supporting the use of one PPI over another)
• the influence of the specialist physician
• lack of knowledge regarding costs of PPIs
• convenience of prescribing certain PPIs (no additional paperwork).

b) Gap #2
Physicians are prescribing double dose PPIs as initial therapy for the management of GERD in up to 31% of patients. The evidence demonstrates that double-dose PPIs are no more efficacious than standard dose PPIs as initial therapy for the management of esophagitis.

Despite a lack of evidence supporting double-dose PPIs for initial therapy, the current practice analysis indicates that high/double-dose PPIs are being prescribed for initial therapy. The evidence-based statement from the Scientific Report supporting this identified gap is:
• Doubling the standard daily doses of PPIs, as initial therapy, is no better than standard daily dose PPI therapy for healing of erosive esophagitis.

In addition, the Scientific Report identified the following research gaps where there is a lack of evidence associated with this gap:
• Double-dose PPIs are more efficacious than standard dose PPIs for patients with uninvestigated GERD symptoms who have severe symptoms.
• Double-dose PPIs are more efficacious than continued standard dose PPIs in patients with uninvestigated GERD, erosive esophagitis or ENRD, who remain symptomatic with regular dose PPIs.
When discussing this gap, focus group participants identified two main reasons as to why they believed physicians might prescribe high/double dose PPIs for initial therapy:

- Anecdotally reported patient benefit, as well as potential benefit, to the busy practitioner by reducing the possibility of a repeat patient visit due to failed therapy.
- The influence of specialists who prescribe PPIs at high/double doses.

In addition, participants expressed disbelief that physicians were prescribing double/high doses of PPIs as initial therapy.

c) **Gap #3**

Physicians would consider prescribing acid suppressive therapy (i.e., PPIs or H$_2$RAs) for treating asthma, cough and laryngeal symptoms associated with GERD. Evidence is lacking to support this practice.

Evidence-based statements supporting this gap include:

- PPIs are not efficacious in improving asthma in patients with concomitant GERD.
- PPIs are not efficacious in improving laryngeal symptoms (i.e., cough, throat clearing, globus, hoarseness, sore throat) associated with reflux.
- PPIs are not efficacious in improving chronic cough with or without GERD.

Despite a lack of evidence supporting the use of PPIs for the treatment of asthma, cough or laryngeal symptoms associated with GERD, the current practice analysis reveals that nearly all physicians would consider prescribing PPIs for such a purpose.

When discussing this gap, focus group participants had three major reactions:

- disbelief that physicians would consider using PPIs in this manner (the majority of participants did not believe that PPIs were appropriate for the treatment of asthma, cough, or laryngeal symptoms not associated with GERD)
- that a lack of evidence does not necessarily mean that there is no clinical benefit; the issue may not have been studied and future research could reveal a benefit
- conviction, based on clinical experience, that PPIs are effective in addressing cough or laryngeal symptoms associated with GERD despite the presented evidence.

In addition, participants reported:

- specialist use of PPIs to treat laryngeal symptoms and cough.

The identification of the gaps in practice, with respect to the prescribing and use of PPIs, allowed for the development of key messages, as well as interventions and tools to address the gaps and ultimately optimize the prescribing and use of PPIs in Canada.

### 10 Key Messages

Potential key messages for the evidence-based statements were developed in which the practical application of the statements was considered given the identified gaps in practice. In other words, what did the evidence-based statements mean to decision and policy makers, prescribers and patients regarding optimizing the prescribing and use of PPIs? Then, a process which ranked the key messages to reveal those that were most relevant was undertaken. The process considered whether or not there was a related practice gap, the strength of the associated evidence, and the original
The ranking process revealed the following three key messages:

1. All PPIs are equally efficacious in the initial treatment of GERD, dyspepsia and other common GI conditions.
2. Doubling the standard daily doses of PPIs, as initial therapy, is no better than standard daily dose therapy.
3. PPIs are not efficacious in treating cough, asthma or laryngeal symptoms associated with GERD.

Additional key messages were developed based on the aforementioned selection process, and may be of interest to jurisdictions:

4. Although H₂RA therapy is effective in managing many patients, standard dose PPIs are superior to H₂RAs in the initial and maintenance management of uninvestigated GERD and erosive esophagitis.
5. Alternatives (PPI discontinuation, H₂RAs, on-demand dosing) to long-term regular use of standard dose PPIs for GERD may be appropriate in selected patients.
6. Step-down therapy (H₂RAs, fh-dose PPI, on-demand PPI and intermittent PPI) in erosive esophagitis leads to relapse.
7. The value of standard dose PPI in the initial and ongoing management of ENRD is questionable, based on currently available evidence.
8. PPIs are preferred in the initial short-term management of uninvestigated dyspepsia, but are no better than H₂RAs for functional dyspepsia.
9. For ongoing maintenance treatment of dyspepsia, therapeutic options include no drug, on-demand H₂RA and on-demand PPI.
10. Patients with duodenal ulcers do not require continuation of PPI therapy after H. pylori eradication.
11. Standard-dose PPIs are efficacious in the treatment and prevention of NSAID-associated ulcers.

11 Interventions Aimed at Influencing Behaviour

Several interventions have been used to encourage the appropriate prescribing of medications. Some of these interventions target physician prescribing behaviour while others are directed toward patients or policy decision makers.

11.1 Professional Interventions

Professional interventions are aimed at improving professional practice and the delivery of effective health services. Professional interventions include educational interventions, audit and feedback, and reminders.

Educational interventions are designed to increase the understanding of clinical care principles or the awareness of specific practice recommendations. These include: the distribution of educational material (electronically published or printed recommendations for clinical care, including clinical practice guidelines and audio-visual materials); educational meetings (gatherings of health care professionals in face-to-face or virtual environments); a local consensus process (a debate and discussion between professionals and other concerned parties toward the establishment of a general consensus on the importance and management of specific clinical problems within a limited, local jurisdiction); educational outreach visits or academic detailing (face-to-face interactions with healthcare providers).
educational meetings between a trained person and a health provider in his or her own setting, aimed at changing the provider’s behaviour); and outreach to local opinion leaders (use of providers nominated by their colleagues).

Audit and feedback is another strategy that has been widely used to optimize physician practice, defined as any summary of clinical performance of health care over a period of time. Audit and feedback may also include recommendations for clinical action. In some cases, health care professionals are passive recipients of feedback, while in other cases, professionals are actively involved and have specific and formal responsibilities for implementing change. The latter method of audit and feedback may have a larger impact on improving professional practice.

Reminders are another method used to help clinicians recall information they already know (or would be expected to know). This method oftentimes presents the information in different, more accessible or relevant formats, or at a particularly appropriate time. Reminders can take different forms, such as:
- cue sheets containing general knowledge or advice, with no patient information or patient-specific advice and not requiring a response
- checklists containing general knowledge or advice, with no patient information or patient-specific advice but requiring response to specific questions
- patient profiles containing patient data and/or patient-specific knowledge or advice; these may also contain general knowledge or advice, but no response is required
- profile checklists containing patient data and/or patient-specific knowledge or advice; one or more of the statements or questions indicate that a response must be recorded.

Reminders can be delivered manually (on paper) and electronically (on screen).

11.2 Disease Management Interventions

Disease management programs are generally designed to improve the process of health care delivery and patient outcomes. Appropriate management of a particular chronic condition may reduce overall treatment costs; for example, a reduction in emergency room visits and hospitalizations, and better choice of medications.

11.3 Policy-related Interventions

Drug plans have undertaken a variety of strategies in an attempt to manage drug utilization and to curb rising prescription costs. Formulary-based interventions (prior authorization and reference pricing) and drug utilization interventions have been tested and used by drug plans in North America.

Prior authorization is widely used by most drug plans in Canada. Different terms such as limited use, special authorization, and exception status have been used to describe prior authorization. Under prior authorization, the drug plan must authorize a prescription for a certain class of drugs before it can be filled. Prior authorization has been used:
- to limit the use of drugs in a certain class to patients with particular medical conditions or complications
- as a means of reinforcing a preferred drug list, where the preferred drug is listed as a general benefit while other drugs in the class require prior authorization
• in combination with a step-up therapy program, so the patient must try a less expensive drug before receiving the drug originally requested.

Reference pricing has also been used to control drug utilization and drug cost. Under a reference-pricing system, a base price is established as a basis for reimbursement. The base price is usually based on the least expensive drug in a particular class. Any amount charged above the reference price is the responsibility of the patient.

Drug utilization review (DUR) is another strategy that has been widely used in North America for monitoring and managing the appropriate use of drugs. Generally, DUR programs review claims data to identify inappropriate prescribing that may lead to adverse medical outcomes. Many programs use interventions based on DUR to influence physician prescribing behaviour. For example, DUR may identify particular physicians who prescribe fewer or more drugs than their peers, or who do not adhere to the treatment guidelines (physician profiling). Once identified, education interventions can be designed and targeted to those physicians.

11.4 Patient Interventions

Patient interventions include educational interventions and patient reminders. Patient educational interventions are defined as those that include formal and structured instruction on a disease and on ways to manage symptoms. Patient education interventions include self-management programs, counselling, leaflets, and small group meetings.4,9

Patient reminders are used to improve patient adherence to medication, screening or vaccination. They can be delivered by a variety of methods (e.g., telephone or mail) and levels of intensity (e.g., single or multiple reminders).

12 Effectiveness of Interventions Intended to Influence Behaviour

The scientific and gray literature was searched and reviewed to identify evidence-based interventions that have been used nationally and internationally to stimulate optimal utilization of PPIs (and/or acid suppressants).4 Twenty-four studies were identified. They were categorized as: professional interventions, disease management interventions, dissemination strategies for dyspepsia guidelines, policy-related interventions, and patient interventions.4

The majority of interventions were multifaceted interventions, regardless of whether the goal was appropriate PPI prescribing, guideline implementation or disease management. The components for these multifaceted interventions vary among studies, leading to difficulty in attributing the effectiveness to particular components. All studies involving multifaceted interventions showed positive impact on outcomes. This was especially evident where passive distribution of educational material was reinforced by interactive educational components such as meetings, educational outreach visits or physician feedback. These findings are compatible with other reviews showing that multifaceted interventions are more likely to succeed than a single intervention.4,9

Formulary-related interventions such as prior authorization and reference-based pricing have been found to be useful in controlling PPI drug expenditure, but long-term impact on health outcomes and drug cost has not been evaluated.
The studies that examined the impact of DUR interventions found that interventions based on drug utilization reviews were effective in changing physician-prescribing behaviour for acid suppressants or PPIs, especially when DUR interventions involve both physicians and pharmacists.

Educating patients about their conditions and when and how to use their medications has been found to be useful in controlling long-term use of PPIs.4

In studies where cost saving was a measured outcome, the cost of the interventions was not calculated or subtracted from the apparent cost saving. This may overestimate the value of the cost saving. None of the studies explored the cost effectiveness of the intervention.

Barriers to implementation were not carefully addressed in most studies included in the review.4 Only one study described physicians’ busy workloads as barriers to intervention implementation. Another study showed that outreach visits that are not targeted to physicians with specific difficulties or barriers had no effect on changing physicians’ behaviours. Identifying barriers to implementation and tailoring interventions to address these barriers may enhance the success of the intervention and improve health care and patient outcomes. Barriers may include lack of hard evidence or lack of communication about evidence-based health care, fear of using the evidence, poor knowledge about the result of their current behaviour, increased workload, lack of time, lack of money and resources, and persistence of the status quo (i.e., the natural tendency to return to previous practice patterns).

In conclusion, the evidence on the best intervention for enhancing appropriate prescribing of PPIs is limited, but the review suggests that combining educational multifaceted interventions with evidence-based formulary intervention may appropriately affect the prescribing of PPIs.4

13 Selection of Interventions

With the evidence on the effectiveness of interventions and the specific evidence related to interventions and PPI prescribing and use behaviour in hand, the Selection of Interventions meeting took place. Representatives from the COMPUS Advisory Committee and the COMPUS Expert Review Panel, as well as experts in the field of behavioural change, were invited to participate.

The objective of the meeting was to recommend a range of interventions aimed at influencing behaviour regarding the prescribing and use of Proton Pump Inhibitors (PPIs) that are appropriate for Canadian jurisdictions:

- Interventions selected are based on evidence showing greatest effect and the capacity of jurisdictions to implement them.
- Recommendations consider different perspectives, including professional behaviour (i.e., physicians and pharmacists), policy decisions, and patient behaviour.

The objectives of the meeting were met through a process whereby the COMPUS key messages were discussed, followed by the identification and exploration of barriers to the realization of the key messages in practice. Once both the key messages and their barriers were acknowledged, target audiences for various interventions were identified. The capacity of the various jurisdictions to use, deliver and support the interventions was also considered. These efforts culminated in the recommendation of specific interventions to be developed by COMPUS to optimize the prescribing and use of PPIs in Canada.
13.1 **Key Messages**

Prior to the meeting, the three Key Messages, together with their associated evidence-based statements, were developed. The participants discussed the identified key messages, and were in general agreement regarding their relevancy and importance. It was noted, however, that there are other key messages associated with the Evidence-Based Statements.

The three key messages considered in the selection of interventions are:

1. All PPIs are equally efficacious in the initial treatment of GERD, dyspepsia and other common GI conditions.
2. Doubling the standard daily doses of PPIs, as initial therapy, is no better than standard daily-dose therapy.
3. PPIs are not efficacious in treating cough, asthma or laryngeal symptoms associated with GERD.

13.2 **Barriers**

Before considering what interventions may be of use when promoting the key messages, it was recognized that the possible barriers to implementing changes in behaviour related to PPI prescribing and use needed to be identified. Understanding potential barriers allows interventions to be specifically designed and targeted to overcome these barriers. A number of potential barriers were discussed including:

- limited information on costs of PPIs for prescribers
- cost information may change over time
- not all PPIs have been approved for all indications
- pre-existing perceptions re: benefits/harms/side-effects/standard dosages
- special populations; e.g., renal patients
- specialist influence on general/family practitioner’s prescribing
- prior experience with PPIs of prescribers or patients (friends, family members), media (direct to consumer advertising)
• medication coverage by drug plans/cost of therapy to patient
• physician time demands
• lack of availability of diagnostic equipment
• physician knowledge gaps.

13.3 Target Audiences

Keeping in mind both the key messages and the potential barriers to behaviour change regarding PPI prescribing and use, the target audiences for different interventions were discussed and identified. The identified target audiences are:
• Prescribers (General/Family Practitioners, Nurse Practitioners (NPs))
• Policy Decision Makers
• Pharmacists
• GI Specialists
• Patients.

13.4 Interventions

Participants discussed the merits and limitations of each intervention, and recommended whether or not COMPUS should undertake their development.

It was recommended that the following interventions be developed:

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<th>Intervention</th>
<th>Target</th>
<th>Tools</th>
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| Educational materials             | Family doctors (and other prescribers), patients, pharmacists and specialists | • Card containing relevant PPI information  
                                   |                                                                        | • Alternative prescription pad  
                                   |                                                                        | • Newsletter |
| Educational meetings              | Family doctors (and other prescribers), pharmacists                     | • Both didactic and interactive presentations                           |
| Educational Outreach (Academic Detailing) | Family doctors (and other prescribers)                          | Academic Detailing (AD) toolkit:  
                                   |                                                                        | • Newsletter  
                                   |                                                                        | • Alternative Prescription/tear-off pad  
                                   |                                                                        | • Laminated information card |
| Audit and Feedback                | Family doctors (and other prescribers)                               | • A self-audit tool                                                   |
| Multifaceted Interventions        |                                                                        | • Combining two or more of the recommended interventions              |

14 Conclusions and Next Steps

PPIs are a class of medications frequently prescribed and widely used in Canada to treat a variety of common gastrointestinal (GI) conditions. Between 2003 and 2004, PPI prescriptions dispensed increased by 15%, from 10.8 million to 12.4 million. However, questions exist about whether PPIs are being prescribed and used appropriately. Both over- and under-usage of PPIs have been reported, and costs associated with inappropriate prescribing and use may be considerable.

Through a defined, multi-step process starting with the evidence, the PPI project has culminated in the selection and development of tools ready for implementation to optimize the prescribing and use of PPIs and ultimately improve health outcomes within Canadian jurisdictions. With input from
the jurisdictions and experts in the field, the evidence has been searched, evaluated and synthesized into evidence-based statements; the current practice related to PPI prescribing and use has been determined; gaps between the evidence (what we know) and the current practice (what we do) have been identified; key messages to address these gaps have been prepared; and evidence-based tools have been selected and developed.

Now, with the support of the members of the COMPUS Advisory Committee, the CADTH Liaison Team, and COMPUS staff, CADTH aims to build and maintain relationships with interventionists in Canada, both for the implementation of interventions relating to the optimal prescribing and use of PPIs, and for future projects.

COMPUS seeks to engage key stakeholders that may include, but is not limited to: professional colleges (continuing medical education programs for physicians and pharmacists); associations (pharmacy and medical, both provincial and national); and private enterprises that provide continuing medical education services. COMPUS key stakeholders are intended to operate independently, without outside influence. Communications with this pivotal group will involve: identification; engagement; opportunities for partnerships, including assistance with material content; and evaluation.

CADTH will work with those interested in using COMPUS materials to facilitate their uptake and implementation. Support for implementation and evaluation will be available through COMPUS.

An evaluation framework will be available to guide the evaluation of interventions and related tools, and COMPUS will assist in bringing groups together within the jurisdictions to aid in the evaluation of the interventions. The framework will contain both quantitative (for determining the effect of interventions on PPI utilization) and qualitative (for determining the effects of the interventions on knowledge, behaviour and attitudes surrounding PPI use and prescribing) components, and will set out approaches to evaluate the impacts of interventions, as well as identify opportunities for quality improvement. The evaluation component of the PPI project will inform stakeholders of the effectiveness of the interventions.

Through the uptake and adoption of COMPUS key messages, health outcomes can be improved and limited health care resources can be targeted more effectively. The pan-Canadian approach to the identification and promotion of optimal drug prescribing and use employed by CADTH, as well as building upon existing optimal use initiatives, reduces duplication of effort and contributes to the quality and effectiveness of the Canadian health care system.
15 References


