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Cost-Effectiveness and Cost-Utility of Long-Term Management Strategies for Heartburn

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ABSTRACT

Objectives: To compare the expected costs and outcomes of seven alternative long-term primary care strategies for the management of patients with moderate-to-severe heartburn over a 1-year period.

Methods: A decision-analytic model was developed to estimate costs and effects (weeks with heartburn symptoms and quality adjusted life years [QALYs]) for each strategy. Meta-analyses were used to synthesize acute treatment and maintenance studies and physician surveys to collect information on patient management. The impact of uncertainty on the base case results was assessed using probabilistic sensitivity analysis. Probability distributions were defined for key model parameters and techniques of Monte Carlo simulation were used to draw values from these distributions. Cost-effectiveness acceptability curves (CEACs) conditional on the monetary value decision makers are willing to pay for a symptom-free day or QALY were created for each strategy.

Results: In the base case, no strategy was strictly dominated by any other strategy. However, two strategies (maintenance H_2-receptor antagonists [H_2RA] and step-down proton pump inhibitor [PPI]) were dominated through principles of extended dominance. The least costly and least effective strategy was intermittent H_2RA, while maintenance PPI was the most costly and most effective.

Conclusions: This analysis showed that the best way of managing patients with heartburn depends on how much society is willing to pay to achieve health improvements. Based on the commonly quoted threshold of $50,000 per QALY, the optimal primary care strategy for managing patients with moderate-to-severe heartburn symptoms is to treat the symptoms with a PPI followed by maintenance therapy with an H_2RA to prevent symptomatic recurrence.

Keywords: cost-effectiveness analysis, cost-utility analysis, economic evaluation, heartburn.

Introduction

Symptoms of gastroesophageal reflux disease (GERD) are highly prevalent [1], and GERD is associated with impaired health-related quality of life. Furthermore, the direct and indirect costs attributed to GERD are substantial [2,3]. Although GERD is mostly managed in primary care, it accounts for 17% of visits to gastroenterologists [4]. Drugs used to treat GERD are widely prescribed and impose a significant burden on government and private insurance plans [5]. In addition, the market for over-the-counter reflux remedies is substantial [6].

For the most part, clinical trials have emphasized the healing and prevention of esophageal erosions as the dominant metric of treatment efficacy in the management of more severe GERD. Previous meta-analyses have evaluated strategies to manage erosive esophagitis [7,8], and published economic models have evaluated acid suppressive therapies using endoscopic end points to select patient cohorts and/or judge treatment success [9,10]. However, the management of GERD in primary care is guided by the presence and absence of symptoms, often without prior referral to a specialist for endoscopic evaluation. Although the symptoms of upper gastrointestinal disease are notoriously nonspecific, heartburn as a dominant complaint is pre-

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dictive of underlying gastroesophageal reflux [11,12].

Current Canadian guidelines endorse primary care empiric management of uncomplicated heartburn without referral or prior investigation [13]. Thus, there is a need to reevaluate primary care management approaches systematically in terms of their effectiveness in relieving symptoms and their overall cost-effectiveness. Strategies based on managing patient symptoms bear greater relevance to clinical practice in primary care, where the majority of gastroesophageal reflux symptoms are managed.

There continues to be controversy regarding the optimal acute treatment and maintenance strategies for managing heartburn. Although proton pump inhibitors (PPI) are superior to H_2-receptor antagonists (H_2RA) and prokinetic agents (PK) in their degree and speed of healing [14], they also have higher acquisition costs. Payers and decision makers must determine whether the additional cost of PPI therapy is justified by its benefits in relieving symptoms and preventing recurrence [10]. Economic analyses based solely on heartburn symptoms have been limited. Heudebert et al. [15] used decision analysis to conclude that empiric treatment strategies dominate strategies requiring initial investigation in the management of GERD. In treating heartburn and acid regurgitation symptoms, an analysis by Gerson et al. [16] found on-demand PPI to dominate on-demand H_2RA as well as maintenance therapy with either H_2RA or PPI. However, the strategies compared in these studies were limited and they did not derive efficacy inputs from a systematic literature review and synthesis. In addition, neither study employed probabilistic sensitivity analysis to address uncertainty in model input parameters.

The objective of this study was to compare, over a 1-year period, the expected costs and outcomes of alternative primary care strategies for the management of patients with moderate-to-severe heartburn. Outcomes are expressed in terms of symptomatic recurrences averted, weeks without heartburn and quality adjusted life years (QALYs) over a 1-year period. Costs are expressed in 2001 Canadian dollars and calculated from the perspective of the provincial government payer for health care. The analytic strategy for the analysis was fivefold: 1) to identify strategies which are dominated by others having both higher costs and worse outcomes; 2) determine if any strategies are dominated through principles of extended dominance; 3) among the remaining nondominated strategies, to estimate incremental costs, effects, QALYs, cost-effectiveness, and cost-utility; 4) to determine the impact of uncertainty in model input parameters on the cost-effectiveness and cost-utility of the heartburn strategies; and 5) using commonly quoted threshold values of cost per QALY, to determine the optimal primary care management strategy for patients with heartburn.

Methods

Overview of Model

A decision-analytic model was used to compare the costs and effects of alternative long-term management strategies for adult patients with moderate to severe heartburn. Strategies varied with respect to the first-line therapy and the second-line therapy for first-line failure or symptom recurrence. The strategies were initially based on a review of the literature and were then refined based on responses from two surveys sent to family physicians and gastroenterologists. The finalized strategies are shown in Table 1 and are discussed below.

Strategy A: Intermittent short course H2RA. Acute treatment with an H_2RA (e.g., ranitidine 150 mg twice daily) for 4 weeks and no further treatment with prescription medications until recurrence.

Strategy B: Intermittent long course H_2RA. Acute treatment with an H_2RA (e.g., ranitidine 150 mg twice daily) for 4 weeks followed by another 4 weeks if symptoms persist, and no further treatment with prescription medications until recurrence.

Strategy C: Intermittent PPI. Acute treatment with a PPI (e.g., omeprazole 20 mg or lansoprazole 30 mg once daily) for 4 weeks and no further treatment with prescription medications until recurrence.

Strategy D: Maintenance H_2RA. Acute treatment with an H_2RA (e.g., ranitidine 150 mg twice daily) for 4 weeks followed by continuous maintenance treatment with an H_2RA (same dose).

Strategy E: Maintenance PPI. Acute treatment with a PPI (e.g., omeprazole 20 mg or lansoprazole 30 mg once daily) for 4 weeks followed by continuous maintenance treatment with a PPI (same dose).

Strategy F: Step-down maintenance H_2RA. Acute treatment with a PPI (e.g., omeprazole 20 mg or

Table 1 Step-up and switching algorithms conditional upon symptomatic relief and recurrence. In the absence of symptom relief, management of initial or recurrent symptoms moves downwards along each algorithm. Maintenance treatment may be included once relief of initial or recurrent symptoms is achieved.

Initial management	Maintenance treatment	Recurrence management	Maintenance treatment
Strategy A: intermittent short course H_2RA			
1) H2RA x 4 wks	None	1) H_2RA x 4 wks	None
2) PPI x 4 wks	None	2) PPI x 4 wks	None
3) DD PPI x 4 wks	PPI	3) DD PPI x 4 wks	PPI
4) DD PPI x 4 wks		4) DD PPI x 4 wks	
5) Surgery		5) Surgery	
Strategy B: intermittent long course H_2RA			
1) H_2RA x 4 wks	None	1) H_2RA x 4 wks	None
2) H_2RA x 4 wks		2) H_2RA x 4 wks	
3) PPI x 4 wks	None	3) PPI x 4 wks	None
4) DD PPI x 4 wks	PPI	4) DD PPI x 4 wks	PPI
5) DD PPI x 4 wks		5) DD PPI x 4 wks	
6) Surgery		6) Surgery	
Strategy C: intermittent PPI			
1) PPI x 4 wks	None	1) PPI x 4 wks	None
2) DD PPI x 4 wks	PPI	2) DD PPI x 4 wks	PPI
3) DD PPI x 4 wks		3) DD PPI x 4 wks	
4) Surgery		4) Surgery	
Strategy D: maintenance H_2RA			
1) H_2RA x 4 wks			
2) PPI x 4 wks	H_2RA	1) PPI x 4 wks	H_2RA
3) DD PPI x 4 wks	PPI	2) DD PPI x 4 wks	PPI
4) DD PPI x 4 wks		3) DD PPI x 4 wks	
5) Surgery		4) Surgery	
Strategy E: maintenance PPI			
1) PPI x 4 wks			
2) DD PPI x 4 wks	PPI	1) DD PPI x 4 wks	PPI
3) DD PPI x 4 wks		2) DD PPI x 4 wks	
4) Surgery		3) Surgery	
Strategy F: step-down maintenance H_2RA			
1) PPI x 4 wks	H_2RA	1) PPI x 4 wks	H_2RA
2) DD PPI x 4 wks	PPI	2) DD PPI x 4 wks	PPI
3) DD PPI x 4 wks		3) DD PPI x 4 wks	
4) Surgery		4) Surgery	
Strategy G: step-down maintenance PPI			
1) PPI x 4 wks	LD PPI	1) PPI x 4 wks	LD PPI
2) DD PPI x 4 wks	PPI	2) DD PPI x 4 wks	PPI
3) DD PPI x 4 wks		3) DD PPI x 4 wks	
4) Surgery		4) Surgery	

Abbreviations: DDPPI, double-dose proton pump inhibitor; H_2RA, H_2-receptor antagonist.

lansoprazole 30 mg once daily) for 4 weeks followed by continuous maintenance treatment with an H_2RA (e.g., ranitidine 150 mg bid).

Strategy G: Step-down maintenance PPI. Acute treatment with a PPI (e.g., omeprazole 20 mg or lansoprazole 30 mg once daily) for 4 weeks followed by continuous maintenance treatment with a low-dose PPI (e.g., omeprazole 10 mg or lansoprazole 15 mg once daily).

Strategies A through G represent primary care strategies (rather than single drugs) for the management of patients with heartburn where the physician increases the dose of the drug or switches to another drug if the patient fails to achieve symptomatic relief or if symptoms recur. The logic of patient management regarding step-up, step-down, or drug switching is shown in Table 1. The strategies differ in the initial management of symptoms and in the maintenance therapy to prevent symptom recurrence. However, there is a consistent logic among the strategies with respect to assumptions about step-up, step-down, and drug switching. For example, failure to achieve symptomatic relief on an H_2RA leads to an attempt to heal with a PPI. Failure to achieve symptomatic relief on regular-dose PPI leads to either a 4-week or 8-week trial of double-dose PPI. Regardless of the intent of initial therapy, if symptom relief requires a double-dose PPI, it is assumed for all strategies that maintenance therapy

would be regular-dose PPI. Finally, if a patient experiences a symptomatic recurrence on any maintenance therapy, it is assumed that higher doses or more effective medication would be required to achieve symptomatic relief.

The overall model structure shown in Figure 1 uses the step-up, step-down, and switching algorithms shown in Table 1. The model quantifies expected costs and outcomes for each strategy, where expected means the sum of costs or outcomes associated with each pathway in the model weighted by their probability of occurring. Therefore, total costs capture both the up-front costs of initial drug therapy and any downstream costs due to maintenance therapy or the management of symptomatic recurrence. A state-transition model with three 4-month cycles was used to model costs and events over a 12-month period.

Outcome Measures

The primary outcome measure used in the analysis was QALYs over 12 months. The utility weight attributed to a day of symptoms with heartburn (0.82) was obtained from a study by Heudebert et al. [15], based on a consensus of experts using a modified Delphi technique. Heartburn-free days were assumed to incur no disutility for patients. In addition to QALYs, symptom-free weeks and heartburn recurrences were also used as measures of effect. Symptom-free weeks have been commonly used for economic evaluations of gastroenterologic interventions as they combine the number of symptom recurrences and the speed with which symptoms are relieved.

A systematic review of published controlled clinical trials was undertaken to derive pooled estimates of symptom relief and recurrence probability for each strategy. Studies published through January 2000 were identified from Medline, CINAHL, and Health STAR using terms reflux, gastroesophageal reflux, esophagitis, GERD, and heartburn. Fully recursive reference searches were performed on all retrieved articles to ensure as comprehensive a search as possible of the published literature. Study inclusion criteria were: English language; adult subjects (i.e., over 16 years of age); randomized controlled trial; single- or double-blind studies; symptom reporting at baseline and scheduled time intervals; and treatment of patients with at least one single-drug therapy. Although the presence or absence of erosive esophagitis is used in most trials, this was not a selection criterion.

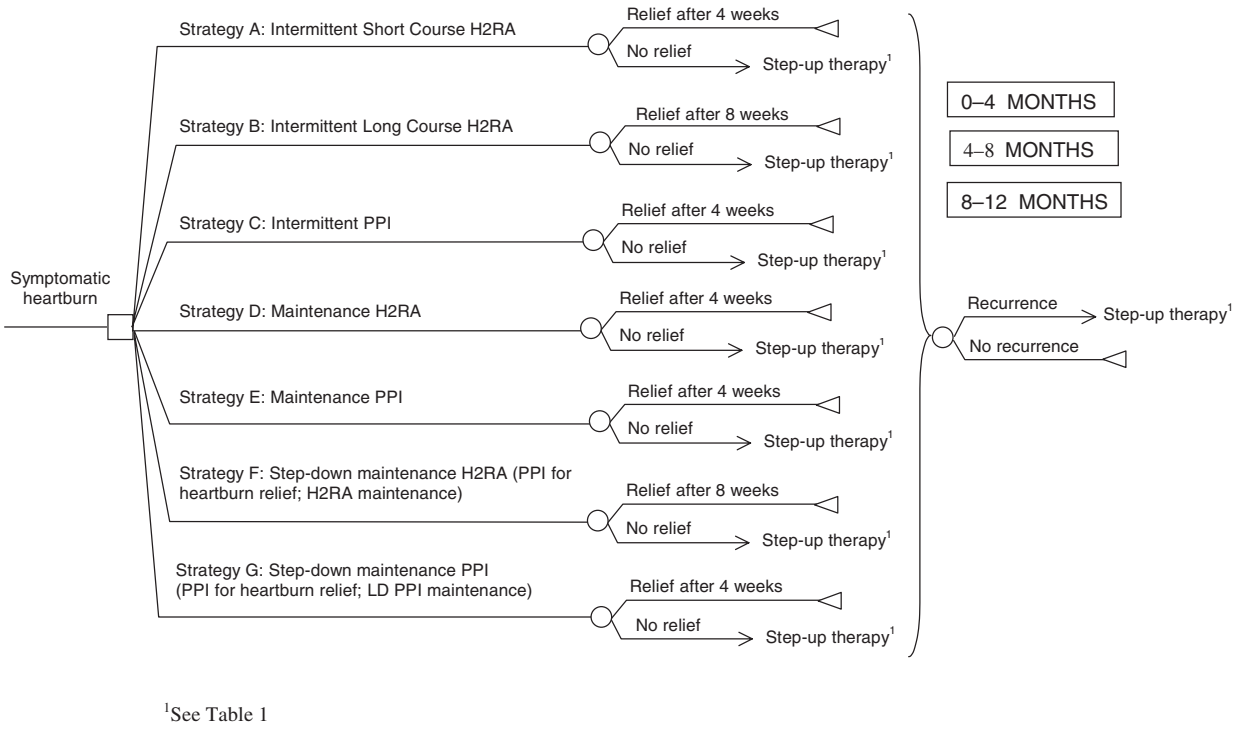

Figure 1 State transition model for the management of symptomatic heartburn.

Symptomatic Relief Analysis

For studies meeting the inclusion criteria, the number of patients with relief from heartburn symptoms (defined as mild or none) at each time interval and the number of patients initially at risk (i.e., intent-to-treat principle) were extracted. Rates of symptomatic relief by drug regimen were estimated using principles of meta-analysis applied to data from single arms of trials pooled together. Details of the methods for calculating rates of symptomatic relief and recurrence are provided in Table 2. Rates of heartburn relief were calculated separately for regular-dose H_2RA (e.g., ranitidine 150 mg twice daily), regular-dose PPI (e.g., omeprazole 20 mg or lansoprazole 30 mg daily), and double-dose PPI (e.g., omeprazole 40 mg or lansoprazole 60 mg daily).

Differences among rates of symptomatic relief across drug regimens were assumed to be normally distributed and were compared using standard Z-scores. The formula used to compare rates of symptomatic relief across drug regimens is also provided in Table 2. Time with heartburn symptoms over the acute relief period for each drug regimen was calculated as the area under the relief curve using standard principles of mathematical integration.

Recurrence Analysis

For studies that met the inclusion criteria, we identified the number of patients initially at risk, and the number of patients with heartburn recurrence (defined as moderate-to-severe heartburn) at regularly scheduled follow-up intervals. Methods for calculating rates of symptomatic recurrence are provided in Table 2. Symptomatic recurrence rates were estimated for the following: placebo (i.e., for intermittent H_2RA and PPI); H_2RA (e.g., ranitidine 150 mg twice daily); regular-dose PPI (e.g., omeprazole 20 mg or lansoprazole 30 mg daily); low-dose PPI (e.g., omeprazole 10 mg or lansoprazole 15 mg daily). To estimate 95% confidence intervals (CI), a random effects model was assumed around the pooled rates of recurrence for each maintenance therapy. Recurrence probabilities at each time interval were compared across therapies using standard Z-scores. The formula used to compare rates of symptomatic recurrence across drug regimens is also provided in Table 2.

Management of Initial and Recurring Symptoms

There are no published data regarding the typical management of patients with moderate-to-severe heartburn symptoms in primary care. Therefore, we

Table 2 Calculation of rates of symptomatic relief and recurrence. Using random effects pooled estimates of events from single arms of RCTs, relief and recurrence rates were estimated assuming exponential and random effects [22–24] models. The mathematical formulae used to perform the relief and recurrence analysis are:

Relief or recurrence	
A_i	Time point of observation for study *i*
n_i	Number of patients evaluated in study *i*
π_i	Proportion relieved/recurred at Time A for study *i*
$V = [\pi_i(1-\pi_i)]/n_i$	Variance of proportion for study *i*
$w_i = 1/V(\pi_i)$	Weight given to observation *i*
$\pi = (\Sigma w_i \times \pi_i)/\Sigma w_i$	Adjusted pooled relief/recurrence rates for treatment group (e.g., PPI-based regimens)
Random effects adjustments	
$RSS = \Sigma\left(w_i \times (\pi - \pi_i)^2\right)$	Residual sum of squares for treatment group
$C_1 = k - 1$	k = number of studies
$C_2 = \Sigma w_i - (\Sigma w_i^2/\Sigma w_i)$	
$S^2 = (RSS - C_1)/C_2$	Estimation of variation between studies in treatment groups
$w_i^* = 1/(V(\pi_i) + S^2)$	Random effects adjusted weight given to observation *i*
$\pi^* = \Sigma(w_i \times \pi_i)/\Sigma w_i^*$	Relief/recurrence rates for treatment groups
$V(\pi^*) = 1/\Sigma w_i^*$	Random effects adjusted variance for treatment groups
$95\%\ C.I. = \pi^* +/- 1.96 \times V(\pi^*)$	95% confidence interval of pooled relief/recurrence rates for treatment groups
$Z = \left(\pi_1^* - \pi_2^*\right)/\sqrt{\left(V\left(\pi_1^* + \pi_2^*\right)\right)}$	Z-score for difference in pooled relief/recurrence rate between treatment groups 1 and 2

conducted two surveys, one of family physicians and one of gastroenterologists. Physicians listed in Ontario in the 1998 Canadian Medical Directory (CMD) were selected at random to participate in the survey. A total of 100 questionnaires were mailed out to family physicians and 65 to gastroenterologists. In both groups there were two physicians listed in the CMD who were no longer practicing. There were 55 family physician and 48 gastroenterologist questionnaires completed and returned for a response rate of 56% and 76%, respectively. Since we assumed that all patients would initially be managed by their family physician, the family physician survey responses were used to determine initial patient management. The gastroenterologist survey responses were used only when the family physician indicated he/she would make a referral.

The survey questionnaires were designed to capture information about the management of patients at initial presentation with heartburn symptoms, after failure of initial therapy, and upon recurrence of heartburn symptoms. The proportions listed in the second column of Table 3 were used to assign costs to the tests and procedures associated with initial patient management. The third and fifth columns were used to cost tests and procedures ordered by family physicians if initial treatment was not effective in relieving symptoms. Finally, the fourth and sixth columns of Table 3 were used to cost out tests and procedures ordered by the gastroenterologist after initial treatment failure and upon referral from the family physician.

A summary of the findings from the surveys of management of symptomatic heartburn recurrence is presented in Table 4. Since physician management of a recurrence might depend on previous diagnosis, we asked about tests and procedures ordered under four different scenarios in both the family physician and gastroenterologist questionnaires: maintenance therapy for patients with previous testing indicating nonerosive reflux disease (NE-GERD); maintenance therapy for patients with previous evidence of erosive gastroesophageal reflux disease (E-GERD); no maintenance therapy for patients with previous testing indicating NE-GERD; no maintenance therapy for patients with previous testing indicating E-GERD.

The columns in Table 4 were used to cost out tests and procedures ordered for symptomatic recurrence. Which column was used for any particular recurrence depended on whether the patient was on maintenance therapy or not, whether the patient had a previous test indicating NE-GERD or E-GERD, and whether the patient was being managed by their family physician or by a gastroenterologist. The proportion of symptomatic patients with subsequent testing indicating NE-GERD or E-GERD was estimated from a review of heartburn relief studies. This proportion was used as a "weight" for NE-GERD or E-GERD patients in the model.

Unit Cost for Health Care Resources

Our primary source of drug price information is the weighted average price per equivalent dose based on scripts from the Intercontinental Medical Statistics (IMS) CompuScript database over a 12-month period ending November 2000. Weighted average prices were determined by multiplying Ontario Drug Benefit (ODB) plan or manufacturer-specific costs by the proportion of prescriptions for each manufacturer. Weighted average prices were calculated separately for regular dose H_2RA, regular-dose PPI, and low-dose PPI. We also applied a standard 10% pharmacy mark-up charge and used a $4.11 dispensing fee for all prescriptions. These are the maximum allowances under the ODB program.

Physician fees for visits and procedures such as

Table 3 Summary of findings from the family physician and gastroenterologist surveys for initial patient management of heartburn symptoms

		Failure of H_2RA (%)		Failure of PPI (%)	
Test/procedure ordered	Initial treatment (%)	FP	GI	FP	GI
CBC	25.5	21.8	37.5	25.0	39.6
Upper GI series	27.3	41.8	6.3	32.7	2.1
Upper GI endoscopy	1.8	21.8	64.6	23.1	89.6
24-hr pH study	0.0	0.0	2.1	1.9	10.4
Testing for *H.pylori*	16.4	27.3	4.2	34.6	4.2
Motility study	0.0	1.8	2.1	0.0	6.3
Referral to GI	0.0	5.5	—	42.3	—

Notes: FP: family physicians (n = 55).
GI: gastroenterologists (n = 48).

Table 4 Summary of findings from the family physician and gastroenterologist surveys for management of symptomatic heartburn recurrence

	Hypothetical patients assumed to be on maintenance therapy (%)				Hypothetical patients assumed not to be on maintenance therapy (%)			
Test/procedure ordered	NE-GERD		E-GERD		NE-GERD		E-GERD	
	FP	GI	FP	GI	FP	GI	FP	GI
CBC	40.0	22.9	65.5	39.6	40.0	25.0	60.0	35.4
Upper GI series	20.0	2.1	18.2	0.0	18.2	2.1	16.4	0.0
Upper GI endoscopy	16.4	2.1	38.2	27.1	9.1	8.3	40.0	25.0
24-hr pH study	7.3	18.8	7.3	8.3	7.3	20.8	7.3	0.0
Test for *H.pylori*	43.6	6.3	41.8	2.1	38.2	4.2	32.7	2.1
Motility study	7.3	12.5	5.5	4.2	7.3	12.5	3.6	2.1
Referral to GI	12.7	—	32.7	—	12.7	—	27.3	—

Notes: FP: family physicians ($n = 55$).
GI: gastroenterologists ($n = 48$).
NE-GERD: previous testing indicated nonerosive gastroesophageal reflux disease.
E-GERD: previous testing indicated erosive gastroesophageal reflux disease.
Abbreviations: CBC, complete blood count; GI, gastrointestinal; *H. pylori*, Helicobacter pylori.

endoscopy were obtained from the Ontario Schedule of Benefits for insured medical services [17]. Nonphysician procedure costs were obtained from a hospital participating in the Ontario Case Costing Project (OCCP) in southwestern Ontario [18]. Drug prices, professional fees, and procedure unit costs used in the analysis are presented in Table 5.

Cost-Effectiveness and Cost-Utility Analyses

The analysis of the state-transition model provides expected costs, expected recurrences, expected weeks with heartburn symptoms, and expected QALYs over a 12-month follow-up period. General principles of cost-effectiveness analysis were applied to these results [19]. First, it was determined whether certain strategies were dominated by other strategies, which had both higher costs and lower therapeutic benefits. Second, it was determined whether any strategies were dominated through principles of extended dominance (i.e., whether linear combinations of other strategies can produce the same (or greater) benefit at lower (or the same) cost). Finally, among nondominated alternatives, incremental cost-effectiveness and cost-utility ratios were calculated using the ratio of the difference in cost to the difference in outcome between the two alternatives. Beginning with the least costly strategy, alternatives were compared with the next most costly strategy to calculate incremental ratios. This process produces what is referred to as efficient frontier of increasingly more costly and more effective strategies. The slope of this frontier reflects incremental cost-effectiveness/utility—the additional cost at which additional units of effect/utility can be purchased.

Table 5 Unit costs for health-care resources

Health-care resource	Cost* (CDN$)
H_2RA regular dose daily weighted average†	0.82
PPI regular dose daily weighted average†	2.33
PPI low dose daily weighted average†	2.13
Family physician general assessment	28.10
Gastroenterologist reassessment	38.65
CBC	4.52
Upper GI series	103.86
Upper GI endoscopy	222.72
24-hr pH study	14.53
Urea breath test for *H.pylori*	4.72
Motility study	99.33
Surgery (Nissen Fundoplication)	3695.60

*Including pharmacy mark-ups and physician fees where appropriate.
†Weighted average price per equivalent dose from IMS CompuScript database (for example, for low-dose PPI, omeprazole 10 mg has 25% of the market, lansoprazole 15 mg has 75% of the market, and pantoprazole 20 mg has less than 1% of the market. The weighted average price would be [omeprazole \$1.75 × 0.25] + [lansoprazole \$2.00 × 0.25] + [pantoprazole \$1.70 × < 0.01] = \$1.94. After adding on a standard 10% pharmacy mark-up, the total weighted cost would be \$2.13).
Abbreviations: CBC, complete blood count; GI, gastrointestinal; *H. pylori*, Helicobacter pylori.

Probabilistic Sensitivity Analyses

The traditional approach used for handling uncertainty in economic evaluations is to conduct deterministic sensitivity analyses of key model parameters where fixed-point estimates of key model parameters are valued one at a time. A recent advance on simple sensitivity analysis is probabilistic sensitivity analysis where one encodes probability distributions rather than point estimates for key model parameters, and one then uses Monte Carlo simulation techniques to make random draws from these distributions for each simulation of the model.

In this study, probability distributions were defined for three sets of key model parameters: symptomatic relief; symptomatic recurrence; resource use for initial symptom relief or symptom

recurrence. In decision theory, it is common to use a Beta distribution to represent an unknown parameter whose value is constrained between 0 and 1 (e.g., a proportion). Therefore, we fitted Beta distributions using the method of moments [20] from the results of the meta-analyses to represent probabilities for symptom relief and symptom recurrence. Beta distributions were also fitted from the family physician and gastroenterologist survey responses to represent ordering of medications, tests and procedures for initial symptomatic relief or upon symptomatic recurrence.

Finally, since drug costs under the ODB plan are fixed across the province and only vary by strength and supplier, we did not feel it was appropriate to define continuous probability distributions for drugs. To reflect drug cost variability across suppliers, we constructed three separate drug-price lists; one for regular dose H_2RAs, one for regular-dose PPIs, and one for low-dose PPIs. The entries in these price lists reflected actual supplier prices and the number of entries in each list for each supplier was weighted according to the actual number of drug prescriptions as reported in the IMS Compuscript database for a 12-month period ending November 2000. In the probabilistic sensitivity analysis, drug prices were randomly selected from these weighted price lists for each separate simulation of the model.

Acceptability Curves and Optimal Heartburn Management

Using the results from the probabilistic sensitivity analysis and the net-benefit framework [21], CEACs were derived for each strategy for different levels, ceiling ratios, of society's willingness to pay per QALY. The commonly quoted threshold of $50,000 per QALY and the range suggested by Laupacis et al. [22] as moderate evidence for adoption of a new technology (i.e., $20,000 to $100,000 per QALY) were then used as benchmarks to determine which strategy would be considered the most cost-effective for managing patients with moderate-to-severe heartburn.

Results

Symptomatic Relief

Studies of heartburn symptomatic relief meeting the study inclusion criteria are shown in Appendix A by drug regimen. The number of patients entering each study along with the percentage of patients achieving symptomatic relief at weeks 2, 4, and 8 are presented. Using these relief studies and the methods described in Table 2 for pooling across studies, the estimated symptomatic relief probabilities are presented in Table 6 by drug regimen. The estimated symptom relief at 4 weeks is 30% for H_2RA, 65% for regular-dose PPI, and 76% for double-dose PPI.

Recurrence Analysis

Studies reporting recurrence of moderate-to-severe heartburn symptoms are shown in Appendix B by drug regimen. The number of patients entering each study and the proportions of patients with recurrence at 3, 6, 9, and 12 months is presented. Based on these studies and the methods described in Table 2 for pooling results across studies, the results of the recurrence analysis are presented in Table 6. These results indicate that the 3-month recurrence rate for regular-dose PPI is the lowest at 8.6%, followed by low-dose PPI at 16.6%, H_2RA at 27.4%, and finally, no therapy (in strategies with no maintenance therapy) at 50.6%. The PPI drug regimens also have the lowest conditional 4-month recurrence rates (4.2 and 3.5%, respectively).

Table 6 Heartburn symptomatic relief and recurrence probabilities by drug regimen

Drug regimen	No. of study arms	Relief / recurrence	
		Symptom relief (%) at:	
		4 weeks (95% CI)	8 weeks* (95% CI)
H_2RA	34	30.0 (25.6, 34.5)	15.7 (8.45, 23.11)
PPI regular dose	29	65.0 (60.5, 69.3)	— —
PPI double dose	11	76.0 (69.0, 82.3)	12.5 (0, 45.8)
		Symptom recurrence (%) at:	
		First 3 months (95% CI)	Every 4 months† (95% CI)
Placebo	5	50.6 (45.2, 55.9)	14.8 (7.9, 22.1)
H_2RA	2	27.4 (21.7, 33.5)	11.8 (7.4, 16.6)
PPI regular dose	6	8.6 (5.9, 11.6)	4.2 (2.5, 6.1)
PPI low dose	6	16.6 13.0, 20.5)	3.5 (1.3, 5.7)

*Conditional probability of symptom relief with 4 additional weeks of therapy.
†Conditional probability of symptomatic recurrence every 4 months following initial 3 months.

Expected Costs and Outcomes

Estimates of the expected costs, expected recurrences, expected weeks with heartburn symptoms, and expected QALYs, are presented in Table 7 by treatment strategy. The intermittent H_2RA strategies have the lowest expected 1-year costs but also have the highest expected number of recurrences, expected number of weeks with heartburn symptoms, and the lowest QALYs. The intermittent long-course H_2RA strategy (B) is less effective than the short-course strategy (A) because with the short course, a larger proportion of patients are switched earlier to the more effective PPI treatment. Maintenance PPI has the highest expected cost per patient over 1 year but also has the lowest expected number of recurrences, expected weeks with heartburn symptoms, and highest QALYs.

The incremental cost-effectiveness and cost-utility results are shown in the last two columns of Table 7. The incremental results show the extra annual cost of one strategy relative to another divided by the extra benefits gained by that strategy relative to the other strategy. In the base case analysis, no treatment strategy was strictly dominated by any other strategy, although strategies D and G were dominated through principles of extended dominance. Using conventional methods for analysis of multiple comparisons (see methods section), the efficient frontier of management of symptomatic heartburn is represented by strategies B, A, C, F, and E. Moving from strategy B to A costs an additional $26 per heartburn symptom week averted, or $7,515 per QALY gained. Moving from strategy A to C costs an additional $42 per symptom week averted (or $12,206 per QALY), from strategy C to F costs an additional $81 per symptom week averted ($23,367 per QALY), and finally from F to E costs an additional $341 per symptom week averted ($98,422 per QALY).

These incremental cost-effectiveness and cost-utility results can be displayed graphically on a plane showing cost and effect or cost and utility pairings. Since the utility weight for a symptom-free day and a day of symptoms are simply scalars for symptom days, the shape of the efficient frontier and relative positioning of pairings was the same for both the cost-effectiveness and cost-utility analyses. Therefore, only the cost-utility plane will be discussed. These results are shown graphically in Figure 2 relative to strategy B. Figure 2 illustrates that the efficient frontier of management for symptomatic heartburn is represented by strategies B, A, C, F, and E. In the base case, strategies D and G are contained within the frontier indicating extended dominance. The slope of the line segments in Figure 2 reflects the incremental cost-utility ratio, or how much it would cost to purchase additional QALYs.

Probabilistic Sensitivity Analysis, Acceptability Curves, and Optimal Management

The results of the probabilistic sensitivity analysis (i.e., 1000 Monte Carlo simulations) are shown graphically in Figure 3. The simulation results in Figure 3 reveal a fair amount of variation from the base case analysis, represented by a solid line. In fact, there are 1000 separate efficiency frontiers, one associated with each separate simulation of the model (not shown in Figure 3). The CEACs for each strategy are presented in Figure 4. These results suggest that for ceiling ratios below $8,000 per QALY, strategy B has the highest probability of being the most cost-effective. For ceiling ratios between $8,000 and $20,000 per QALY, strategy D is likely to be the most cost-effective. Between $20,000 and $115,000 per QALY, strategy F is likely to be the most cost-effective. Finally, for ceiling ratios above $115,000 per QALY, strategy E

Table 7 Base-case expected cost, recurrences, weeks with heartburn symptoms and incremental cost-effectiveness

Strategy	Expected 1-year cost per patient	Expected recurrences per patient in 1 year	Expected weeks with heartburn symptoms	Expected QALYs	Incremental cost per heartburn week averted* (CDN$)	Incremental cost per QALY* (CDN$)
B. Intermittent long course H_2RA	815	0.540	11.64	0.883	—	—
A. Intermittent short course H_2RA	888	0.559	8.86	0.892	26†	7,515
C. Intermittent PPI	1,005	0.523	6.10	0.902	42	12,206
F. Step-down maintenance H_2RA	1,076	0.301	5.21	0.905	81	23,367
E. Maintenance PPI	1,334	0.117	4.46	0.908	341	98,422
D. Maintenance H_2RA	982	0.315	7.65	0.897	Dominated through extended dominance	
G. Step-down maintenance PPI	1,286	0.173	4.71	0.907		

*Relative to the next less costly nondominated strategy. Values have been rounded.
†Example calculation (888–815)/(11.64–8.86) = 26.26.
Abbreviations: DDPPI, double-dose proton pump inhibitor; H_2RA, H_2 receptor antagonist; PPI, proton pump inhibitor; QALY, quality-adjusted life year.

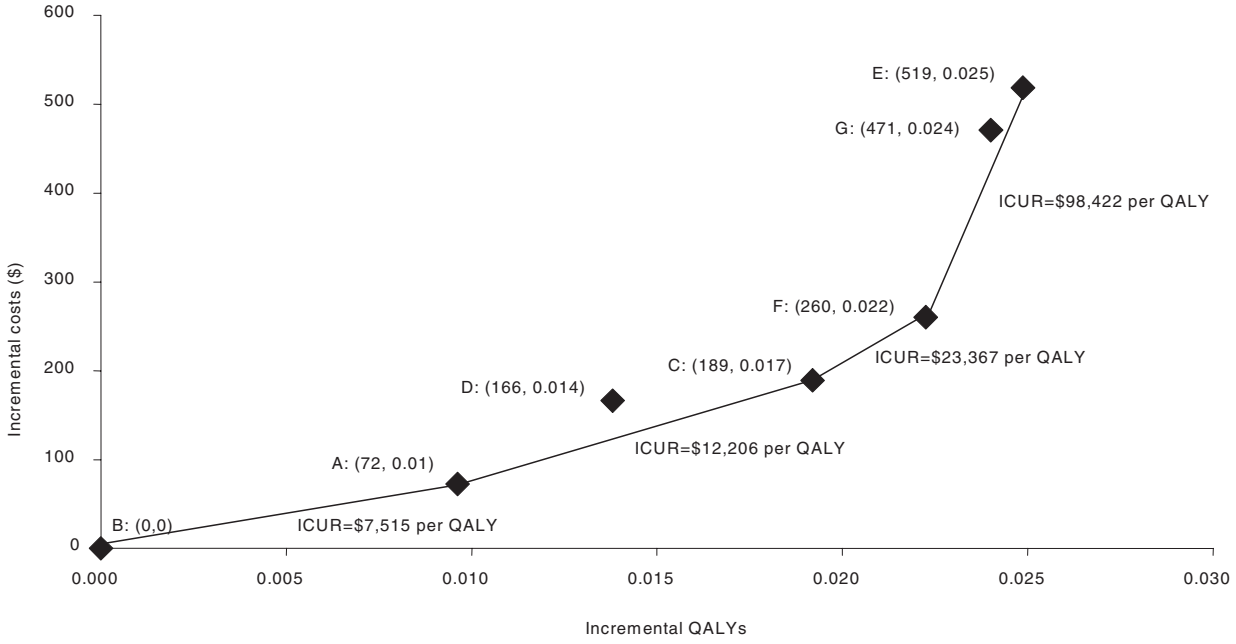

Figure 2 Incremental costs and effects relative to intermittent long course H_2RA (strategy B).

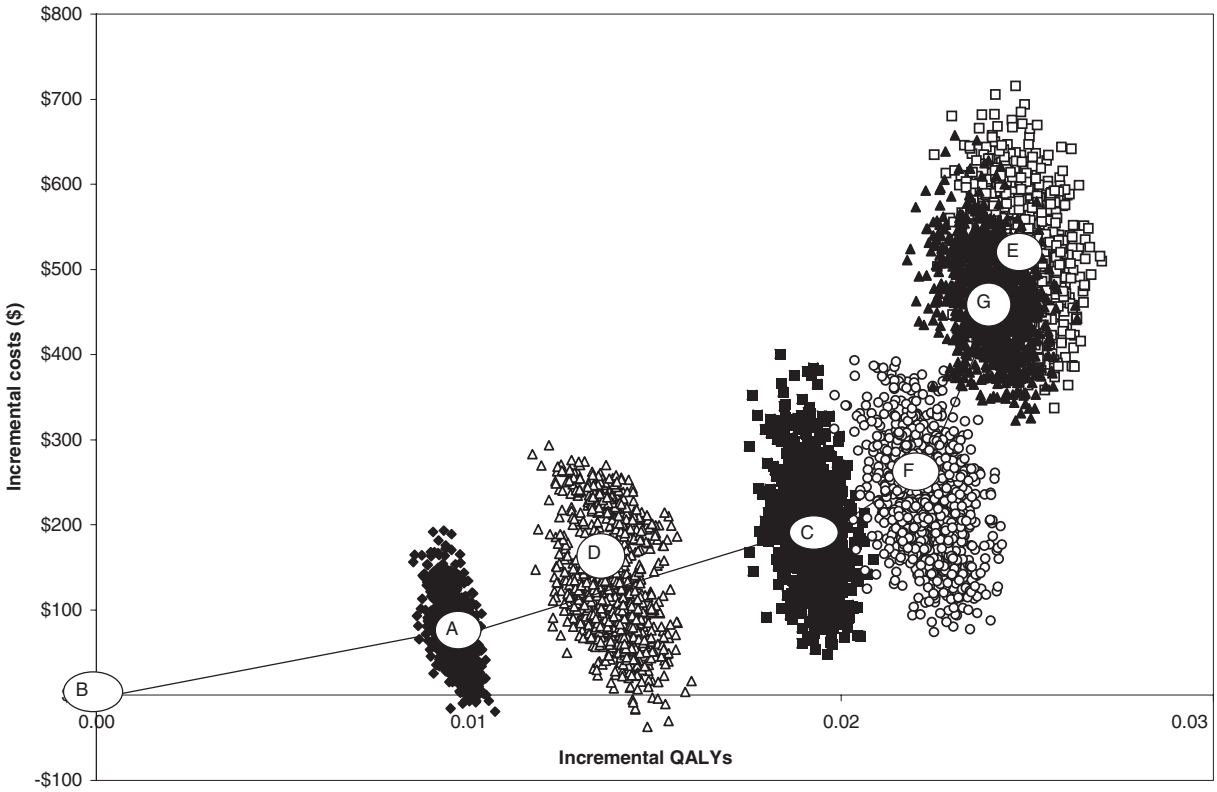

Figure 3 Probabilistic sensitivity analysis: incremental costs and QALYs from 1000 Monte Carlo simulations.

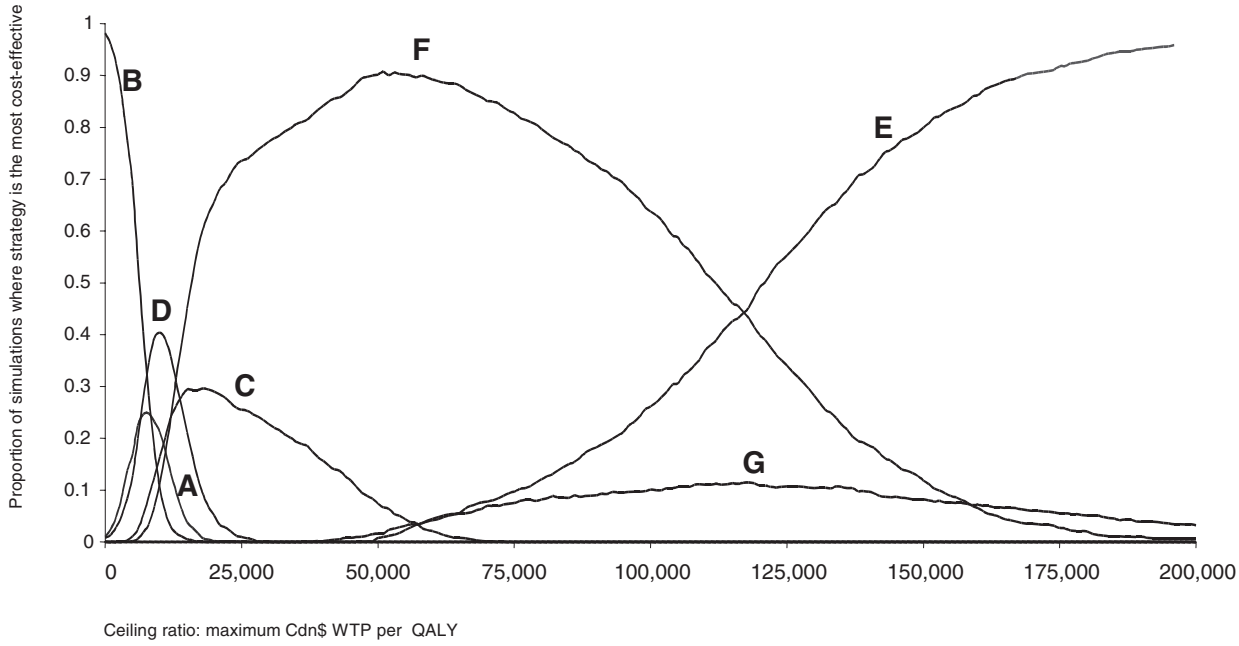

Figure 4 Cost-utility acceptability curves.

is the most cost-effective. Using the threshold of $50,000 per QALY, the optimal primary care management for patients with moderate-to-severe heartburn is strategy F (PPI for relief followed by H_2RA prophylaxis). In fact, strategy F remains optimal throughout the range suggested by Laupacis et al., as moderate evidence for adoption of a new technology (i.e., $20,000 to $100,000 per QALY).

Discussion

A decision-analytic model was constructed to compare the expected costs and outcomes of seven alternative long-term management strategies for patients presenting with moderate-to-severe heartburn. General principals of cost-effectiveness analysis with multiple strategies were used to compare the expected costs and outcomes of each strategy. Using probability distributions for symptom relief, for symptom recurrence, and rates for ordering tests and procedures, we were able to explore the true impact of uncertainty and joint uncertainty across model-input parameters on expected costs and outcomes. The results from the probabilistic simulation analysis provide results that are both qualitatively and quantitatively superior to results obtained from previous studies using traditional deterministic sensitivity analyses.

Of the seven strategies evaluated for the management of heartburn, none were strictly dominated by any other strategy in the base case analysis. Conventional rules for the analysis of multiple comparisons would lead to the conclusion that strategies D and G should be eliminated through principles of extended dominance (i.e., linear combinations of other strategies), and that the efficient frontier for heartburn management is represented by strategies B, A, C, F, and E. Results from the probabilistic sensitivity analysis showed that the optimal management strategy depends on the maximum amount society is willing to pay to achieve health improvements. In other words, there is a trade-off between additional cost and improved health benefits. Based on the commonly quoted threshold of $50,000 per QALY, the optimal primary care management strategy is to prescribe a PPI to relieve symptoms followed by a H_2RA to prevent symptomatic recurrence.

The vast majority of published economic evaluations in GERD have used endoscopic end points to select patients and/or to judge treatment success [9,10]. However, GERD is managed primarily by family physicians according to symptoms and often without referral or endoscopic evaluation. Two recent studies have focused specifically on heartburn-predominant GERD symptoms. One result from our analysis is similar to the findings of Heudebert et al. [15], who reported a cost and QALY trade-off between intermittent H_2RA and intermittent PPI of $10,440 per QALY. This com-

pares to our analysis where we estimate the switch (A to C) would cost $12,206 per QALY. A major limitation of the Heudebert analysis, which prevents a more direct comparison of study findings, is that the study omitted the commonly used step-down strategy of PPI for symptom relief followed by maintenance H_2RA.

Our results do not support the findings of Gerson et al. [16], who found PPI-on-demand (intermittent) to dominate intermittent H_2RA, maintenance H_2RA, and maintenance PPI strategies. The primary reason for these discrepant findings is that Gerson et al. assumed a lower failure rate for intermittent PPI (42% vs. 51%), a higher failure rate for maintenance H_2RA (50% vs. 27%), and a higher failure rate for maintenance PPI (20% vs. 9%).

As with all modeling studies, a number of limitations of the present study are noteworthy. First, we have assumed standardized management strategies for patients presenting with heartburn symptoms (Table 1 and Fig. 1) based on survey responses from 55 family physicians and 48 gastroenterologists. Although physicians who participated in the survey were randomly selected from across Ontario, it is unclear how generalizeable their responses are. It is likely that there are geographic differences in practice patterns, in waiting times for specialist referral, and in the timely availability of diagnostic tests and procedures such as endoscopy. Second, for the symptom relief and symptom recurrence meta-analyses, the majority of studies relied on endoscopy results as a primary entry criterion and outcome measure, and symptoms were typically a secondary criterion. When enough symptom-based studies are available, it would be worthwhile to update the meta-analyses and compare the results.

Third, we used moderate-to-severe heartburn as our primary measure of GERD symptoms. This was primarily because of differences across studies in how GERD symptoms are measured and which symptoms are included in the analysis. Since heartburn is the predominant symptom of GERD, most studies include a separate reporting of heartburn symptoms. It is uncertain how the results of this study might change if a different or more inclusive symptom definition was used. Fourth, the 1-year time horizon chosen for the study may be too short to capture long-term complications such as Barrett's esophagus or esophageal stricture. Given the lack of long-term follow-up studies, we did not feel it was appropriate to extrapolate the model much beyond 1 year. Finally, this study uses inputs (i.e., costs), which are specific to the province of Ontario. Price weights and surveys of practice patterns from other geographic areas would be needed to fully explore the potential impact of regional variations in cost and practice patterns.

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Appendix A: Studies reporting relief of moderate-to-severe heartburn symptoms

Drug	Reference	N	Relief at baseline (%)	Relief at 2 weeks (%)	Relief at 4 weeks (%)	Relief at 8 weeks (%)
Cim400qid	Bate, 1997 [26]	109	0 (0)	34 (31)		
Cim400qid	Dehn, 1990 [27]	36	1 (3)	13 (36)	17 (47)	17 (47)
Cim400qid	Bate, 1990 [278]	138	15 (11)		50 (36)	51 (37)
Cim400qid	Hameeteman, 1987 [29]	21	4 (19)		11 (52)	13 (62)
Cim400qid	Wesdorp, 1978 [30]	12	0 (0)			5 (42)
Cim400qid	Bright-Asare, 1980 [31]	20	0 (0)	11 (55)	14 (70)	15 (75)
Cim400qid	Tytgat, 1987 [32]	21	4 (19)		11 (52)	13 (62)
Fam20bid	Sabesin, 1991 [33]	137	1 (1)	14 (10)	19 (14)	55 (40)
Fam20bid	Robinson, 1991 [34]	158	3 (2)	14 (9)	30 (19)	
Fam40od	Robinson, 1991 [34]	155	3 (2)	6 (4)	16 (10)	
Fam40od	Sabesin, 1991 [33]	135	2 (1)	10 (7)	14 (10)	41 (30)
Ran150bid	Hungin, 1993 [35]	209	3 (1)		50 (24)	
Ran150bid	Bate, 1991 [36]	138	6 (4)		55 (40)	68 (49)
Ran150bid	Londong, 1992 [37]	78	0 (0)		24 (31)	19 (24)
Ran150bid	Klinkenberg-Knol, 1987 [38]	26	0 (0)	6 (23)	8 (31)	
Ran150bid	Vantrappen, 1988 [39]	30	0 (0)		6 (20)	9 (30)
Ran150bid	Koop, 1995 [40]	83	2 (2)	36 (43)	39 (47)	
Ran150bid	Johnson, 1989 [41]	69	2 (3)		35 (51)	
Ran150bid	Bianchi Porro, 1992 [42]	30	0 (0)		6 (20)	13 (43)
Ran150bid	Maton, 1999 [43]	161	0 (0)		60 (37)	71 (44)
Ran150bid	Bardhan, 1999 [44]	229	0 (0)	60 (26)		
Ran150bid	Kahrilas, 1999 [45]	136	0 (0)		48 (35)	54 (40)
Ran150bid	Bardhan, 1995 [46]	77	14 (18)		30 (39)	
Ran150bid	Dakkak, 1994 [47]	21	3 (14)	11 (52)	6 (29)	7 (33)
Ran150bid	Havelund, 1988 [48]	82	3 (4)		30 (37)	
Ran150bid	Italian, 1991 [49]	86	0 (0)		41 (48)	
Ran150bid	Richter, 1996 [50]	97	5 (5)	11 (11)	12 (12)	38 (39)
Ran150bid	Schaub, 1986 [51]	10	0 (0)			4 (40)

Drug	Reference	N	Relief at baseline (%)	Relief at 2 weeks (%)	Relief at 4 weeks (%)	Relief at 8 weeks (%)
Ran150bid	Venables, 1995 [52]	326	0 (0)		130 (40)	
Ran150bid	Bovero. 1987 [53]	60	5 (8)		20 (33)	
Ran150bid	Simon, 1987 [54]	19	1 (5)		6 (32)	16 (84)
Ran300od	Johnson, 1991 [55]	138	0 (0)		50 (36)	52 (38)
Ran300od	Johnson, 1991 [55]	140	0 (0)		50 (36)	61 (44)
Ran300od	Bovero. 1987 [53]	57	1 (2)		20 (35)	
H_2RA		**3244**	**78 (2)**	**192 (18)**	**942 (31)**	**622 (41)**
Om20od	Hungin, 1993 [35]	214	6 (3)		118 (55)	
Om20od	Bate, 1991 [36]	142	10 (7)		94 (66)	102 (72)
Om20od	Venables, 1995 [52]	330	0 (0)		201 (61)	
Om20od	Galmiche, 1997 [56]	141	0 (0)		92 (65)	
Om20od	Hetzel, 1988 [57]	82	15 (18)	51 (62)	62 (76)	
Om20od	Bianchi Porro, 1992 [42]	30	0 (0)		18 (60)	20 (67)
Om20od	Sontag, 1992 [58]	93	12 (13)	41 (44)	55 (59)	66 (71)
Om20od	Mossner, 1995 [59]	95	0 (0)	70 (74)	81 (85)	
Om20od	Bate, 1993 [60]	313	13 (4)		220 (70)	115 (73)
Om20od	Robinson, 1993 [61]	92	18 (20)	44 (48)	55 (60)	66 (72)
Om20od	Corinaldesi, 1995 [62]	105	4 (4)	80 (76)	86 (82)	
Om20od	Bardhan, 1999 [44]	221	0 (0)	122 (55)		
Om20od	Hatlebakk, 1999 [63]	161	0 (0)	59 (37)	71 (44)	76 (47)
Om20od	Bate, 1997 [26]	112	0 (0)		74 (66)	
Om20od	Maton, 1999 [43]	156	0 (0)		98 (63)	104 (67)
Om20od	Dekkers, 1999 [64]	97	0 (0)		59 (61)	64 (66)
Om20od	Bate, 1996 [65]	98	0 (0)		50 (51)	
Om20od	Bate, 1990 [28]	134	13 (10)		94 (70)	93 (69)
Om20od	Carlsson, 1998 [66]	225	23 (10)		153 (68)	
Om20od	Italian, 1991 [49]	86	3 (3)		49 (57)	
Om20od	Laursen, 1992 [67]	110	2 (2)		70 (64)	72 (65)
Om20od	Richter, 1996 [50]	100	17 (17)	33 (33)	46 (46)	74 (74)
Lan30od	Robinson, 1995 [68]	23	1 (4)			14 (61)
Lan30od	Bardhan, 1995 [45]	77	7 (9)		61 (79)	
Lan30od	Mulder, 1996 [69]	106	11 (10)		95 (90)	
Rab20od	Dekkers, 1999 [64]	97	0 (0)		60 (62)	66 (68)
Pan40od	Mossner, 1995 [59]	191	5 (3)	121 (63)	149 (78)	
Pan40od	Corinaldesi, 1995 [62]	103	4 (4)	79 (77)	91 (88)	
Pan40od	Koop, 1995 [40]	166	5 (3)	99 (60)	127 (77)	
PPI		**3900**	**169 (4)**	**799 (57)**	**2429 (66)**	**932 (67)**
Om40od	Hetzel, 1988 [57]	82	10 (12)	60 (73)	63 (77)	
Om40od	Laursen, 1992 [67]	109	0 (0)		71 (65)	89 (82)
Om40od	Lundell, 1990 [70]	51	4 (8)		44 (86)	46 (90)
Om40od	Sontag, 1992 [58]	91	16 (18)	48 (53)	62 (68)	71 (78)
Om40od	Vantrappen, 1988 [39]	31	3 (10)		22 (71)	22 (71)
Om40od	Dehn, 1990 [27]	31	3 (10)	21 (68)	26 (84)	23 (74)
Om40od	Havelund, 1988 [48]	80	1 (1)		61 (76)	
Om40od	Mulder, 1996 [69]	105	16 (15)		96 (91)	
Om60od	Klinkenberg-Knol, 1987 [38]	25	1 (4)	17 (68)	23 (92)	
Lan60od	Bardhan, 1995 [46]	25	7 (9)		54 (72)	
Lan60od	Robinson, 1995 [68]	25	4 (15)			22 (81)
PPI-Double dose		**707**	**65 (9)**	**146 (64)**	**522 (77)**	**273 (80)**

Appendix B: Studies reporting recurrence of moderate-to-severe heartburn symptoms

Drug	Reference	N	Recurrence at 3 months (%)	Recurrence at 6 months (%)	Recurrence at 9 months (%)	Recurrence at 12 months (%)
Placebo	Bate, 1995 [70]	72	27 (38)	39 (54)	47 (65)	48 (67)
Placebo	Hegarty, 1997 [712]	90	32 (36)		38 (42)	49 (54)
Placebo	Laursen, 1995 [72]	30	21 (70)			
Placebo	Robinson, 1996 [734]	55	26 (47)	26 (47)	36 (65)	36 (65)
Placebo	Sontag, 1996 [75]	47	37 (79)	37 (79)	37 (79)	37 (79)
Placebo		**294**	**143 (49)**	**102 (59)**	**158 (60)**	**170 (64)**
R150bid	Hallerback,1994 [76]	128	41 (32)	54 (42)	60 (47)	70 (55)
R150bid	Hegarty, 1997 [72]	90	20 (22)		27 (30)	30 (33)
H_2RA		**218**	**61 (28)**	**54 (42)**	**87 (40)**	**100 (46)**
L15od	Gough, 1996 [77]	91				9 (10)
L15od	Robinson, 1996 [74]	59	12 (20)	12 (20)	13 (22)	17 (29)
L15od	Sontag, 1996 [75]	50	11 (22)	12 (24)	17 (34)	18 (36)
O10od	Bate, 1995 [71]	60	5 (8)	10 (17)	11 (18)	14 (23)
O10od	Hallerback,1994 [76]	133	21 (16)	37 (28)	44 (33)	51 (38)
O10od	Laursen, 1995 [73]	63	20 (32)			
PPI-Low dose		**456**	**69 (19)**	**71 (24)**	**85 (28)**	**109 (28)**
L30od	Gough, 1996 [77]					6 (7)
L30od	Robinson, 1996 [74]	56	3 (5)	9 (16)	17 (30)	18 (32)
L30od	Sontag, 1996 [75]	49	8 (16)	9 (18)	12 (24)	17 (35)
O20od	Bate, 1995 [71]	68	4 (6)	7 (10)	10 (15)	12 (18)
O20od	Hallerback,1994 [76]	131	14 (11)	26 (20)	28 (21)	37 (28)
O20od	Laursen, 1995 [73]	67	7 (10)			
PPI-Regular dose		**448**	**36 (10)**	**51 (17)**	**67 (22)**	**90 (23)**