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Economic Evaluation of Long Term Management Strategies for Erosive Oesophagitis

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Abstract

Objective: To compare the expected costs and outcomes of alternative strategies for the management of patients with erosive oesophagitis.

Design: There were 3 components to the overall analytic approach. First, a decision model was constructed to compare expected costs and outcomes of 6 management strategies. Second, principles of quantitative literature review and meta-analysis were used to determine probabilities of clinical events (i.e. oesophagitis healing and recurrence). Finally, principles of cost-effectiveness analysis were used to compare treatment alternatives in terms of dominance and incremental cost effectiveness. The viewpoint for the study was that of a provincial government payer for healthcare over a 1-year period.

Main outcome measures and results: Healing rates were significantly higher for proton pump inhibitors (PPI) [$p < 0.001$]. Recurrence rates were significantly higher for intermittent therapy (placebo) and lower for regular dose PPI ($p < 0.001$). Maintenance prokinetic agent (PA) is dominated (i.e. more costly and less effective) and step-down maintenance PPI is dominated through principles of extended dominance. The 'efficient frontier' is represented by: maintenance H_2-receptor antagonist (H_2RA), intermittent PPI, step-down maintenance H_2RA and maintenance PPI.

Conclusions: The price of H_2RA is a key factor influencing whether step-down maintenance PPI forms part of, or is contained within, the 'efficient frontier' of long term management for erosive oesophagitis.

Gastro-oesophageal reflux disease (GORD) is a common condition that results from regurgitation of acid from the stomach into the oesophagus. The most frequent symptom of GORD is heartburn, which has been reported to occur daily in up to 10% of the adult population.[1] Some studies indicate that up to 44% of the general population experience heartburn at least once a month.[1-5] While patients with mild heartburn may respond to lifestyle modifications and antacids, the majority of patients with GORD require additional pharmacological therapy to reduce gastric acid secretion. Currently, the choice of first-line antisecretory therapy is between H_2-receptor antagonists (H_2RAs) such as ranitidine and cimetidine and proton pump inhibitors (PPIs) such as omeprazole.

Although they have a higher acquisition cost, PPIs have been found to be more efficacious than H_2RAs in terms of both the rate and speed of healing.[6,7] Faced with the prospect of new medications such as the PPIs that offer increased benefits at an increased cost, many government payers for medicines, such as the national formulary in Australia[8] and the provincial formulary in Ontario, Canada,[9] now require evidence of cost effectiveness (i.e. value for money) before granting reimbursement status to new pharmaceutical products under these programmes. Similar concerns have been voiced in the US, both in terms of reimbursement for interventions under federal programmes such as Medicare[10] and, more recently, in the context of healthcare reform and the growth of managed care.

The objective of this study was to compare, over a 1-year period, the expected costs and outcomes of alternative drug treatment strategies for the management of patients with erosive oesophagitis (i.e. grades 2 to 4 using the Savary-Miller Scale endoscopic classification) confirmed by endoscopy but without complications such as Barrett's oesophagus or stricture. Outcomes are quantified in terms of GORD recurrence and weeks per year without GORD as indicated by data from clinical trials on healing of oesophagitis.

The analytic strategy for the cost-effectiveness analysis was 2-fold: (i) to eliminate 'dominated' strategies which are associated with higher costs and worse outcomes than other alternatives; and (ii) among remaining (nondominated) strategies, to estimate incremental costs, effects and cost effectiveness.

Methods

Overview of Analytic Approach

There are 3 key components to our analytic approach. The first was to structure the therapeutic decision problem using principles of clinical decision analysis. This is a conventional approach to clinical economic modelling[11] where clinical events and costs of relevant strategies are compared using a decision tree. Second, for calculating expected costs and outcomes, we used principles of quantitative literature review and meta-analysis to determine the probabilities of relevant clinical events (i.e. oesophagitis healing and recurrence rates). Finally, principles of cost-effectiveness analysis[12] were used for comparing treatment strategies in terms of weak and strong dominance and incremental cost effectiveness. Sensitivity analysis was also used to explore key areas of uncertainty.

The primary viewpoint of the study was that of a provincial government payer for healthcare and all costs are presented in 1998 Canadian dollars ($Can).

We modelled strategies that embodied different combinations of first-line agents and change of therapy was conditional upon failure to heal oesophagitis or conditional upon its recurrence. The following 6 therapeutic strategies were considered.

Strategy A: Intermittent PPI

Acute treatment with a PPI [e.g. omeprazole 20mg once daily (od)] for 8 weeks and then no further treatment with prescription medications until recurrence.

Strategy B: Maintenance PPI

Acute treatment with a PPI (e.g. omeprazole 20mg od) for 8 weeks and then continuous maintenance treatment with a PPI (same dose).

Table I. Step-up and switching algorithms conditional upon oesophagitis healing failure or recurrence

Healing		Maintenance		1st recurrence	Healing		Maintenance		1st recurrence
Strategy A: intermittent PPI					**Strategy B: maintenance PPI**				
PPI	→	No therapy	→	PPI to heal	PPI	→	PPI	→	DD PPI to heal
↓ unhealed					↓ unhealed				
DD PPI	→	PPI	→	DD PPI to heal	DD PPI	→	PPI	→	DD PPI to heal
Strategy C: maintenance H_2RA					**Strategy D: step-down maintenance PA**				
H_2RA	→	H_2RA	→	DD H_2RA	PA	→	LD PA	→	PA to heal
↓ unhealed					↓ unhealed				
PPI	→	H_2RA	→	PPI to heal	PPI	→	LD PA	→	PPI to heal
↓ unhealed					↓ unhealed				
DD PPI	→	PPI	→	DD PPI to heal	DD PPI	→	PPI	→	DD PPI to heal
Strategy E: step-down maintenance H_2RA					**Strategy F: step-down maintenance PPI**				
PPI	→	H_2RA	→	PPI to heal	PPI	→	LD PPI	→	PPI to heal
↓ unhealed					↓ unhealed				
DD PPI	→	PPI	→	DD PPI to heal	DD PPI	→	PPI	→	DD PPI to heal

DD H_2RA = double dose H_2-receptor antagonists (e.g. ranitidine 300mg twice daily); **DD PPI** = double dose proton pump inhibitor (e.g. omeprazole 40mg once daily); **H_2RA** = H_2-receptor antagonists (e.g. ranitidine 150mg twice daily); **LD PA** = low dose prokinetic agent (e.g. cisapride 10mg twice daily); **LD PPI** = low dose proton pump inhibitor (e.g. omeprazole 10mg once daily); **PA** = prokinetic agent (e.g. cisapride 10mg 4 times daily); **PPI** = proton pump inhibitor (e.g. omeprazole 20mg once daily).

Strategy C: Maintenance H_2RA

Acute treatment with an H_2RA [e.g. ranitidine 150mg twice daily (bid)] for 8 weeks and then continuous maintenance treatment with an H_2RA (same dose).

Strategy D: Step-Down Maintenance Prokinetic Agent

Acute treatment with a prokinetic agent (PA) [cisapride 10mg 4 time daily (qid)] for 12 weeks and then continuous maintenance treatment with a lower dose of PA (cisapride 10mg bid).

Strategy E: Step-Down Maintenance H_2RA

Acute treatment with a PPI (e.g. omeprazole 20mg od) for 8 weeks and then continuous maintenance treatment with a H_2RA (e.g. ranitidine 150mg bid).

Strategy F: Step-Down Maintenance PPI

Acute treatment with a PPI (e.g. omeprazole 20mg od) for 8 weeks and then continuous maintenance treatment with a lower dose PPI (e.g. omeprazole 10mg od).

Alternatives A to F represent clinical strategies (rather then single drugs) for the management of erosive oesophagitis where the physician is assumed to increase the dose of a drug or switch to another drug if the patient fails to respond to the first-line treatment. The logic of these assumptions regarding stepping-up dosage or switching can be found in table I. There is a consistent logic between the strategies with respect to assumptions about step-up and switching. For example, failure to heal on a H_2RA or PA leads to an attempt to heal with a PPI. Failure to heal on regular dose PPI (e.g. omeprazole 20mg), either as first-line or switched therapy, is followed by a further 8-week trial with a double dose of PPI (e.g. omeprazole 40mg). Regardless of the initial therapy's intent, upon healing with double dose PPI, it is assumed that maintenance therapy would be a regular dose of PPI. Finally, if a patient experiences a recurrence on any maintenance therapy, we assume higher doses or more effective medication would be used.

Although not analysed as a first-line strategy, our model allows for drug-refractory patients to receive surgery in the form of laparoscopic (Nissen) fundal plication. To arrive at this option, we assume a patient will have recurrent GORD while on continuous maintenance PPI and will have subsequently failed to be healed on a 8-week course of double dose PPI. Failure to be controlled on omeprazole 40mg is considered by some sur-

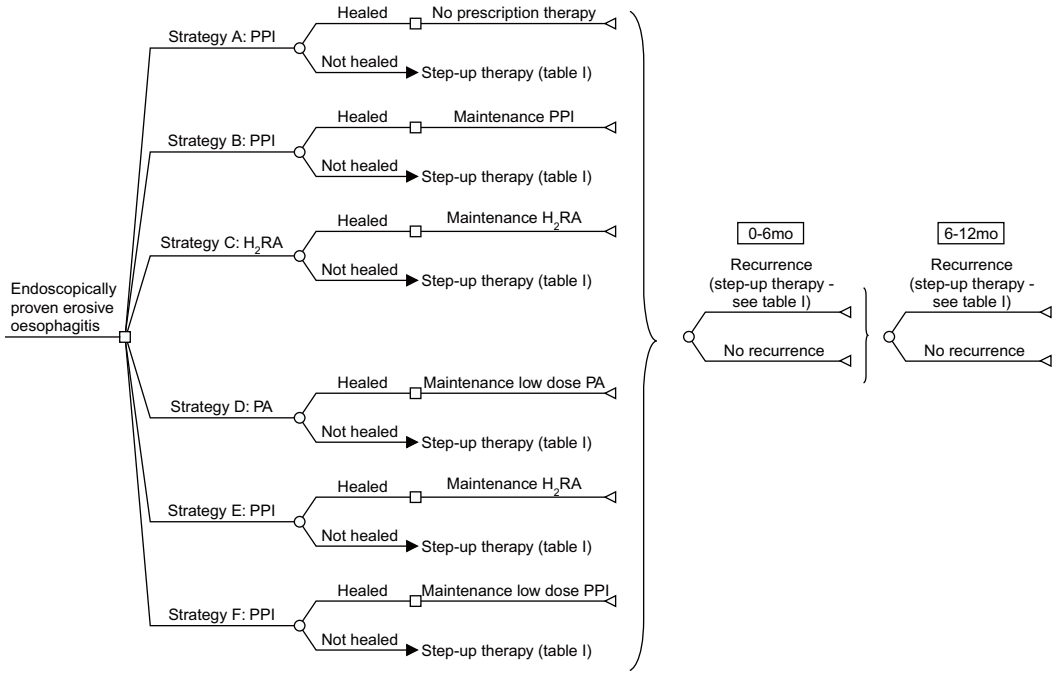

Fig. 1. Decision tree for the management of erosive oesophagitis. **H_2RA** = H_2-receptor antagonist; **PA** = prokinetic agent; **PPI** = proton pump inhibitors.

geons to be a criterion for surgical referral.[13] Our selected strategies are broadly consistent with recommendations from the Ontario Drug Benefit (ODB) Program and the recent Canadian consensus statement on the management of GORD.[14]

The structure of the decision tree shown in figure 1 is based on the treatment strategies and the step-up switching algorithms in table I. The decision analytic model quantifies expected costs and clinical outcomes for each strategy, where 'expected' means a sum of costs and outcomes associated with each branch of the decision tree weighted by their probability of occurrence. Hence, on the cost side, we captured both the 'up-front' costs of initial drug therapy (excluding the confirmatory endoscopy which is common to all strategies) and any 'downstream' costs due to management of GORD recurrence in the 1-year interval. The model structure is recursive in two 6-month periods; hence, probabilities of recurrence in the period to 12 months are conditional upon recurrence or non-recurrence in the period from 0 to 6 months.

Outcome Measures and Clinical Study Selection

In reviewing outcome measurement in acid-related diseases with a specific focus on measurement for economic evaluation, Sintonen[15] recommends that results be expressed in terms of numbers and populations achieving specified targets of success. For GORD, the most commonly used formulation of outcome for economic evaluation has been either oesophagitis-free or symptom-free time in a period of follow-up. The advantage of such a measure is that it combines 2 important aspects of efficacy: (i) the speed with which oesophagitis is healed; and (ii) the likelihood of oesophagitis recurring. The second advantage of this approach is that data are usually available for most GORD treatments on speed of

healing and risk of recurrence while on maintenance therapy.

The general method for combining healing and recurrence probabilities to estimate GORD-free time has been presented by Sintonen and Alander[16] in their earlier appraisal of omeprazole. For this analysis, the primary outcome is GORD-free time during the 12-month period of the model. GORD-free time is defined as time where the oesophagitis is healed. We recognise that this measure is not synonymous with patients being free from GORD symptoms, but it is the outcome that has been most frequently and consistently measured by endoscopy in GORD treatment trials.

Healing and recurrence studies published to November 1997 were identified through Medline using terms gastro-oesophageal reflux, oesophagitis, GORD, clinical trial, randomised controlled trial with the individual drug names of each H_2RA, PA and PPI. 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; adults (i.e. over 16 years of age); single or double-blind studies; studies using endoscopy to assess patients at baseline, at scheduled healing time intervals (for healing studies) and at symptomatic recurrence or at scheduled recurrence time intervals (for recurrence studies); patients with erosive oesophagitis (i.e. grades 2 to 4 using the Savary-Miller scale endoscopic classification); and patients treated with at least 1 single-drug therapy. Studies that included patients with all grades of oesophagitis were included only if it was possible to determine healing or recurrence for patients with grades 2 to 4 oesophagitis.

Healing Analysis

For studies meeting the inclusion criteria, the number of patients healed at each time interval and the number of patients initially at risk (i.e. intent-to-treat principle) were extracted. Rates of healing by drug regimen were estimated using principles of meta-analysis applied to data from single arms of trials pooled together; specifically, we estimated an inverse exponential model of cumulative risk of healing based on the assumption of random effects to estimate a constant hazard healing rate for each drug regimen[17-19] (see table II). Healing curves were estimated for the following drug regimens: PA (e.g. cisapride 10mg qid); regular dose H_2RA (e.g. ranitidine 150mg bid); double dose H_2RA (e.g. ranitidine 300mg bid); regular dose PPI (e.g. omeprazole 20mg od); and double dose PPI (e.g. omeprazole 40mg od).

Table II. Calculation of constant hazard healing rates and statistical analyses of hazard rates

A_i	Time point of observation for study i
n_i	Number of patients evaluated in study i
π_i	Proportion healed at time A for study i
$\lambda_i = -\ln(1 - \pi_i)/A_i$	Healing rate for study i
$V(\lambda_i) = \pi_i/[(1 - \pi_i) \times n_i \times A_i 2]$	Variance of healing rate for study i
$w_i = 1/V(\lambda_i)$	Weight given to study i
$\lambda = (\Sigma w_i \times \lambda_i)/\Sigma w_i$	Summary healing rate (constant hazard) for drug regimen
Random effects adjustments	
$RSS = \Sigma[w_i \times (\lambda - \lambda_i)^2]$	Residual sum of squares for drug regimen
$S^2 = [RSS - (k - 1)]/[\Sigma w_i - (\Sigma w_i 2/\Sigma w_i)]$	Estimation of variation between studies for drug regimen
$w_i^* = 1/[V(\lambda_i) + S^2]$	Random effects weight given to study i
$\lambda^* = \Sigma(w_i^* \times \lambda_i)/\Sigma w_i^*$	Random effects healing rate for drug regimen
$V(\lambda^*) = 1/\Sigma w_i^*$	Random effects variance of healing rate for drug regimen
95% CI = $\lambda^* \pm 1.96 \times V(\lambda^*)$	95% confidence interval of healing rate for drug regimen
$Z = (\lambda^*_1 - \lambda^*_2)/\sqrt{[V(\lambda^*_1 + \lambda^*_2)]}$	Z-score for difference in healing rate between drug regimen 1 and 2

Differences between hazard rates from the healing curves for each drug regimen were assumed to be normally distributed and were compared using standard z-scores. Time without GORD over the acute healing period for each drug regimen was calculated simply as the area under the parabolas defining the GORD healing curves. These areas were estimated by standard principles of mathematical integration of the area under the healing curve for each drug regimen.

Recurrence Analysis

For studies meeting the inclusion criteria, we identified the number of patients initially at risk, the number of patients with endoscopic recurrence during the first 6 months of follow-up and, if available, the number of patients with endoscopic recurrence during the second 6 months of follow-up. For the recurrence analysis, a per protocol approach (i.e. number of recurrences divided by the number of patients evaluated) was used rather than an intention-to-treat approach because, for recurrences, this approach results in more conservative recurrence rate estimates.

Pooled recurrence rates for each maintenance therapy were estimated using a simple unweighted analysis of the number of patient recurrences and the number of patients evaluated summed across all studies. Recurrence rates from 0 to 6 months and 6 to 12 months were estimated for: placebo (i.e. for intermittent PPI); PA (e.g. cisapride 10mg bid); H_2RA (e.g. ranitidine 150mg bid); regular dose PPI (e.g. omeprazole 20mg od); and low dose PPI (e.g. omeprazole 10mg od). Random effects were assumed for estimating 95% confidence intervals (CI) around the pooled rates of recurrence for each maintenance therapy. Recurrence probabilities at 6 and 12 months were compared across therapies using standard z-scores.

Table III. Drug acquisition costs (excluding dispensing fees) and unit prices for nonpharmaceutical healthcare resources

Healthcare resource	Cost ($Can)
Cisapride 10mg	0.61
Ranitidine 150mg (generic)	0.44
Ranitidine 150mg (brand name Zantac®)	1.20
Omeprazole 20mg	2.42
Omeprazole 10mg	1.93
Lansoprazole 30mg	2.20
Lansoprazole 15mg	2.20
Pantoprazole 40mg	2.09
Family physician general reassessment	28.10
Family physician minor assessment	16.25
Gastroenterologist consultation	105.40
Gastroenterologist reassessment	38.65
Gastroenterologist partial assessment	23.10
Upper GI endoscopy	118.22
Upper GI series	141.43
Barium swallow	135.10
Cardiac stress test	84.81
ECG	42.77
Laparoscopic fundal plication	2462.60

$Can = Canadian dollars.

Unit Prices and Recurrence Management

For drugs where a generic equivalent is available, generic prices were used in the base-case analysis. This is a reasonable assumption for drugs such as ranitidine, for example, because market research data indicate that approximately 90% of all scripts dispensed for ranitidine are now generic rather than for the brand name Zantac® [Intercontinental Medical Statistics (IMS)]. Our primary source of drug price information is the best available price (BAP) from the ODB Program[20] with a 10% pharmacy mark-up charge. For omeprazole 10mg, which is not a formulary benefit, the cost was obtained directly from the manufacturer (Astra Pharma Inc., Mississauga, Ontario, Canada). Drug acquisition costs per tablet are presented in table III. In the analysis, a dispensing fee of $Can4.11 was used (i.e. ODB Program) fee of $Can6.11 less a $Can2.00 patient copayment).

In Ontario, hospitals receive global budgets and most physicians are reimbursed by the provincial government on a fee-per-item-of service basis. Cost estimates for physician fees and procedure costs such as endoscopy were estimated from 2 sources: (i) the physician fee schedule for Ontario;[21] and (ii) a hospital participating in the Ontario Case Costing Project (OCCP) in Southwest-

Table IV. Healthcare utilisation and costs of managing recurrence[a]

Healthcare resources	First recurrence		Second recurrence	
	no./%	cost ($Can)	no./%	cost ($Can)
Visits to family physician	2.5	52.48	2.5	52.48
Visits to gastroenterologist	1.5	50.20	1.5	50.20
Barium swallow	7%	9.46	0%	
Cardiac stress test	3.5%	2.97	1%	0.85
ECG	3.5%	1.50	1%	0.43
Upper GI endoscopy	10%	11.82	60%	70.93
Upper GI series	7%	9.90	8%	11.31
Cost per recurrence (excluding drugs)		138.33		186.20

a Practice pattern information obtained from O'Brien et al.[23] Unit prices have been updated for this analysis.

$Can = Canadian dollars.

ern Ontario.[22] Procedure unit costs and professional fees are also presented in table III.

To estimate the costs associated with the management of patients with symptoms of GORD recurrence, information on clinical practice patterns and resource utilisation (e.g. diagnostic test ordering) is required. Since no published data are available on how physicians manage GORD recurrence in Canada, data from our previous study,[23] based on convening an expert physician panel (4 gastroenterologists, 2 family doctors) and using a modified Delphi technique,[24] was used to derive estimates of various services used when patients present with symptoms of GORD recurrence. The panel was first mailed a questionnaire on resource use based on a written scenario of GORD recurrence and then brought together in a committee to discuss their estimates. The main focus was on the likelihood of using expensive investigations such as upper GI series or endoscopy.

The estimates of healthcare utilisation from the physician panel and the results of combining these utilisation data with updated unit costs are presented in table IV. These are 'per recurrence' cost estimates and are used in the model conditional upon recurrence under each management strategy.

Cost Effectiveness and Sensitivity Analyses

Following the evaluation of the decision tree to estimate expected costs and expected weeks without GORD in the 12-month period, general principles of cost-effectiveness analysis were applied.[25] The analytic approach was 3-fold. First, it was determined whether some strategies were dominated by others having both lower costs and greater therapeutic benefits. Second, it was determined if 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 same) cost]. Finally, among nondominated alternatives, incremental cost-effectiveness ratios were calculated using the ratio of the difference in cost to the difference in outcome between 2 alternatives. Beginning with the least costly strategy, alternatives were compared with the next most costly strategy when calculating incremental ratios. This process produces an 'efficient frontier' of increasingly more costly, but more effective, strategies. The slope of this frontier reflects incremental cost-effectiveness – the additional cost at which additional units of effects can be purchased.

Sensitivity analyses were conducted to assess the impact of uncertainty surrounding key model assumptions. We explored uncertainty in both clinical probability estimates and also cost parameters. The following sensitivity analyses were conducted:

- 95% CIs for GORD healing probabilities
- 95% CIs for GORD recurrence probabilities
- generic cimetidine cost and brand name ranitidine (Zantac®) cost for H_2RA
- lansoprazole and pantoprazole costs for PPI

Table V. Gastro-oesophageal reflux disease healing studies by drug class and dose size

Study	Dose	n (ITT)	No. of pts healed at 4wk (%)	No. of pts healed at 6wk (%)	No. of pts healed at 8wk (%)	No. of pts healed at 12wk (%)
Baldi et al.[27]	CIS 10mg qid	15				8 (53)
Galmiche et al.[28]	CIS 10mg qid	11		0 (0)		4 (36)
Geldof et al.[29]	CIS 10mg qid	33			8 (24)	10 (30)
Lepoutre et al.[30]	CIS 10mg qid	11			3 (27)	8 (73)
Maleev et al.[31]	CIS 10mg qid	16				11 (69)
Geldof et al.[29]	CIS 20mg bid	39			7 (18)	20 (51)
Richter & Long[32]	CIS 10mg qid	33				11 (33)
Richter & Long[32]	CIS 20mg bid	40				17 (43)
Robertson et al.[33]	CIS 10mg qid	13				5 (38)
PA		**211**		**0 (0)**	**18 (22)**	**94 (45)**
Elsborg & Jorgensen[34]	C 400mg bid	28	7 (25)			16 (57)
Farup et al.[35]	C 400mg bid	14			3 (21)	
Fiasse et al.[36]	C 400mg bid	10			2 (20)	
Maleev et al.[31]	C 400mg bid	20				11 (55)
Breen et al.[37]	C 200mg tid, 400 hs	10			2 (20)	
Galmiche et al.[38]	C 200mg tid, 400 hs	24		8 (33)		11 (46)
Bate et al.[39]	C 400mg qid	116	25 (22)		36 (31)	
Dehn et al.[40]	C 400mg qid	31	9 (29)		7 (23)	
Galmiche et al.[28]	C 400mg qid	13		4 (31)		3 (23)
Hameeteman et al.[41]	C 400mg qid	20			2 (10)	
Maleev et al.[31]	C 400mg qid	22				12 (55)
McCarty-Dawson et al.[42]	C 800mg bid	231	85 (37)		120 (52)	157 (68)
Palmer et al.[43]	C 800mg bid	93		47 (51)		62 (67)
Wesdorp et al.[44]	C 400mg qid	13			4 (31)	
Bardhan et al.[45]	R 150mg bid	59	21 (36)		26 (44)	
Bianchi-Porro et al.[46]	R 150mg bid	30	6 (20)		10 (33)	
Bremner et al.[47]	R 150mg bid	25			6 (24)	
Feldman et al.[48]	R 150mg bid	35	11 (31)	14 (40)	12 (34)	
Geldof et al.[29]	R 150mg bid	38			17 (45)	24 (63)
Goy et al.[49]	R 150mg bid	18		3 (17)		
Guslandi et al.[50]	R 150mg bid	14		4 (29)		
Havelund et al.[51]	R 150mg bid	47	12 (26)		18 (38)	21 (45)
The Italian Reflux Oesophagitis Study Group[52]	R 150mg bid	86	37 (43)		53 (62)	
Johnson et al.[53]	R 150mg bid	59	17 (29)		30 (51)	
Klinkenberg-Knol et al.[54]	R 150mg bid	26	7 (27)		10 (38)	
Koop et al.[55]	R 150mg bid	83	39 (47)		46 (55)	
Lehtola et al.[56]	R 150mg bid	13		5 (38)		7 (54)
Masci et al.[57]	R 150mg bid	11	4 (36)			
McCarty-Dawson et al.[42]	R 150mg bid	236	90 (38)		132 (56)	168 (71)
McKenna et al.[58]	R 150mg bid	172			94 (55)	112 (65)
Pace et al.[59]	R 150mg bid	36				0 (56)
Richter et al.[60]	R 150mg bid	62			25 (40)	
Robinson et al.[61]	R 150mg bid	127	64 (50)	80 (63)	86 (68)	
Sandmark et al.[62]	R 150mg bid	77	23 (30)		33 (43)	
Schaub et al.[63]	R 150mg bid	8			2 (25)	
Sherbaniuk et al.[64]	R 150mg bid	37			23 (62)	
Simon et al.[65]	R 150mg bid	172		76 (44)		107 (62)
Sontag et al.[66]	R 150mg bid	54	20 (37)		16 (30)	
Sontag et al.[67]	R 150mg bid	75		41 (55)		

Vantrappen et al.[68]	R 150mg bid	30	13 (43)		15 (50)	
Wesdorp et al.[69]	R 150mg bid	19		7 (37)		11 (58)
Zeitoun et al.[70]	R 150mg bid	80	33 (41)		45 (56)	
H_2RA regular dose		**2374**	**523 (36)**	**289 (48)**	**875 (48)**	**742 (64)**
Euler et al.[71]	R 150mg qid	105	48 (46)		73 (70)	83 (79)
Lundell[72]	R 300mg bid	47		8 (17)	18 (38)	22 (47)
McCarty-Dawson et al.[42]	R 150mg qid	229	112 (49)		153 (67)	176 (77)
Pace et al.[59]	R 300mg bid	39				13 (33)
Roufail et al.[73]	R 150mg qid	109	47 (43)		68 (62)	78 (72)
Schaub et al.[63]	R 300mg bid	8			2 (25)	
Silver et al.[74]	R 300mg bid	260	72 (28)		118 (45)	148 (57)
Silver et al.[74]	R 150mg qid	261	93 (36)		145 (56)	172 (66)
Euler et al.[71]	R 300mg qid	105	49 (47)		65 (62)	77 (73)
Roufail et al.[73]	R 300mg qid	120	50 (42)		73 (61)	83 (69)
H_2RA double dose		**1283**	**471 (40)**	**8 (17)**	**715 (57)**	**852 (69)**
Bate et al.[39]	O 20mg od	122	68 (56)		86 (70)	
Bianchi-Porro et al.[46]	O 20mg od	30	15 (50)		23 (77)	
Castell et al.[75]	O 20mg od	431	343 (80)	370 (86)	375 (87)	
Hatlebakk et al.[76]	O 20mg od	113	73 (65)		96 (85)	
Hetzel et al.[77]	O 20mg od	82	57 (70)		65 (79)	
The Italian Reflux Oesophagitis Study Group[52]	O 20mg od	86	44 (51)		63 (73)	
Mee & Rowley[78]	O 20mg od	283	172 (61)		216 (76)	
Mossner et al.[79]	O 20mg od	95	67 (71)		81 (85)	
Richter et al.[60]	O 20mg od	64			51 (80)	
Robinson et al.[80]	O 20mg od	92	63 (68)		75 (82)	
Sandmark et al.[62]	O 20mg od	73	46 (63)		56 (77)	
Sontag et al.[81]	O 20mg od	93	32 (34)		61 (66)	
Zeitoun et al.[70]	O 20mg od	76	56 (74)		66 (87)	
Bardhan et al.[45]	L 30mg od	58	45 (78)		51 (88)	
Castell et al.[75]	L 30mg od	422	336 (80)	361 (86)	368 (87)	
Feldman et al.[48]	L 30mg od	68	51 (75)	56 (82)	59 (87)	
Hatlebakk et al.[76]	L 30mg od	116	71 (61)		95 (82)	
Mee & Rowley[78]	L 30mg od	282	186 (66)		226 (80)	
Mulder et al.[82]	L 30mg od	106	91 (86)		99 (93)	
Robinson et al.[61]	L 30mg od	115	94 (82)	106 (92)	105 (91)	
Robinson et al.[83]	L 30mg od	23	20 (87)	21 (91)	22 (96)	
Sontag et al.[66]	L 30mg od	105	73 (70)		84 (80)	
Koop et al.[55]	P 40mg od	166	103 (62)		122 (73)	
Mossner et al.[79]	P 40mg od	191	126 (66)		153 (80)	
PPI regular dose		**3292**	**2232 (69)**	**914 (86)**	**2698 (82)**	
Dent[84]	O 20-40mg od	31	25 (81)			
Dehn et al.[40]	O 40mg od	29	16 (55)		20 (69)	
Havelund et al.[51]	O 40mg od	49	33 (67)		40 (82)	43 (88)
Hetzel et al.[77]	O 40mg od	82	67 (82)		70 (85)	
Lundell[72]	O 40mg od	51		32 (63)	44 (86)	46 (90)
Mulder et al.[82]	O 40mg od	105	83 (79)		95 (90)	
Sontag et al.[81]	O 40mg od	91	39 (43)		65 (71)	
Vantrappen et al.[68]	O 40mg od	31	23 (74)		25 (81)	
Klinkenberg-Knol et al.[54]	O 60mg od	25	19 (76)		22 (88)	
Bardhan et al.[45]	L 60mg od	55	35 (64)		42 (76)	
Robinson et al.[83]	L 60mg od	27	20 (74)	23 (85)	24 (89)	
PPI double dose		**576**	**360 (69)**	**55 (71)**	**447 (82)**	**89 (89)**

bid = twice daily; **C** = cimetidine; **CIS** = cisapride; **H_2RA** = H_2-receptor antagonist; **hs** = at bedtime; **ITT** = intention to treat; **L** = lansoprazole; **n** = number of pts; **O** = omeprazole; **od** = once daily; **P** = pantoprazole; **PA** = prokinetic agent; **PPI** = proton pump inhibitors; **pts** = patients; **R** = ranitidine; **tid** = 3 times daily; **qid** = 4 times daily.

- average Ontario dispensing fee of $Can9.80 for patients not receiving a drug benefit.[26]

Results

Healing Probabilities and Healing Curves

GORD healing studies meeting the study inclusion criteria are presented in table V. The number of patients entering each study along with the number of patients healed at each scheduled endoscopic assessment are provided and grouped by drug class and dose size. Individual healing percentages for each study are also provided. For the PA studies, the healing rate at 12 weeks was used for input into the healing curve model (table II). For all other drug regimens, healing rates at 8 weeks were used. If healing rates at 8 weeks were not available, the rates at 6 or 12 weeks were used.

Using these healing studies and the healing curve model, the estimated healing probabilities at different time points are presented in table VI by drug regimen (i.e., drug class and dose size). As shown in table VI, the estimated healing rate at 8 weeks is 30% for PA, 43% for H_2RA, 54% for double dose H_2RA, and 82% for PPI or double dose PPI. The cumulative healing curves by drug regimen are illustrated in figure 2. The constant hazard rate (healing curve) for PA is significantly lower than the rate for each of the other drug regimens ($p < 0.001$). The difference between the healing curves for H_2RA and double dose H_2RA is of marginal statistical significance ($p = 0.054$) and the healing curves for PPI and double dose PPI are surprisingly similar ($p = 0.70$). However, both the PPI and double dose PPI curves are significantly higher than either of the H_2RA curves ($p < 0.001$).

The results of integrating the healing curves over various time points (i.e. for estimating weeks with GORD over the healing period) are also presented in table VI. The estimated number of weeks with GORD over the healing period is 9.22 for PA, 6.11 for H_2RA, 5.59 for double dose H_2RA, 3.86 for PPI and 3.80 for double dose PPI. The higher number of weeks with GORD for PA reflects both an overall lower healing rate and a longer acute treatment period (i.e. 12 weeks with PA *vs* 8 weeks with H_2RA or PPI).

Recurrences

GORD recurrence studies meeting the study inclusion criteria are presented in table VII and results are summarised in table VIII. Based on these studies, the recurrence rate at 6 months is 65% for placebo (intermittent PPI), 23% for PA, 38% for H_2RA, 12% for regular dose PPI and 25% for low dose PPI. The recurrence rate at 6 months for placebo is significantly higher than all other maintenance strategies ($p < 0.001$). The recurrence rate for H_2RA is significantly higher than PPI ($p < 0.001$) and PA ($p = 0.01$). The recurrence rate for

Table VI. Healing probabilities and estimated number of weeks with GORD over healing period, by drug regimen

Drug regimen	No. of study arms	Constant hazard rate (95% CI)[a]	GORD healing probabilities[b] at:			Weeks with GORD[c] at:		
			4wk	8wk	12wk	4wk	8wk	12wk
PA (e.g. cisapride 10mg qid)	9	0.05 (0.03, 0.06)		0.30	0.42	3.66	6.72	9.22
H_2RA regular dose (e.g. ranitidine 150mg bid)	42	0.07 (0.06, 0.08)	0.25	0.43	0.57	3.49	6.11	[d]
H_2RA double dose (e.g. ranitidine 300mg bid)	10	0.10 (0.07, 0.12)	0.32	0.54	0.68	3.32	5.59	[d]
PPI regular dose (e.g. omeprazole 20mg od)	24	0.21 (0.19, 0.23)	0.57	0.82	0.92	2.70	3.86	[d]
PPI double dose (e.g. omeprazole 40mg od)	11	0.22 (0.19, 0.25)	0.58	0.82	0.93	2.68	3.80	[d]

a The constant hazard rate (λ) calculations are found in table II.

b The healing rates are calculated using the following equation: proportion healed at week $t = 1 - e^{-\lambda t}$.

c Does not include additional weeks with GORD for patients not healed with first course of H_2RA, PPI or PA.

d The acute treatment period for H_2RA and PPI used in the model is 8 weeks.

bid = twice daily; **CI** = confidence interval; **GORD** = gastro-oesophageal reflux disease; **H_2RA** = H_2-receptor antagonist; **od** = once daily; **PA** = prokinetic agent; **PPI** = proton pump inhibitors; **qid** = 4 times daily.

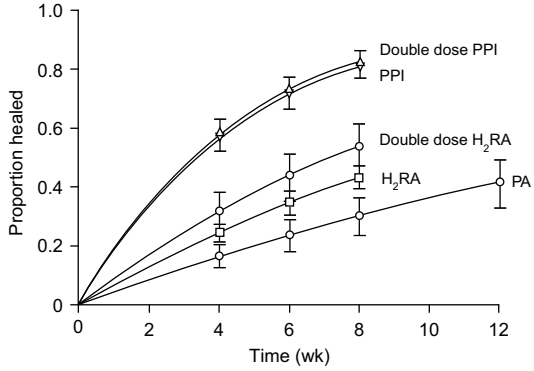

Fig. 2. Cumulative healing curves by drug regimen (error bars are ± 95% confidence intervals). **H_2RA** = H_2-receptor antagonist; **PA** = prokinetic agent; **PPI** = proton pump inhibitors.

low dose PPI is similar to PA but is significantly higher than PPI ($p = 0.001$).

For patients not experiencing a recurrence in the first 6 months of follow-up, the probability of recurrence in the next 6 months is 23% for placebo, 13% for PA, 18% for H_2RA, 8% for regular dose PPI and 13% for low dose PPI.

Expected Costs and Outcomes

Estimates of expected costs and outcomes over 1 year are presented in table IX. For each of the 6 strategies, we present the expected cost per patient, the expected number of GORD recurrences per patient and the expected number of weeks with (and without) GORD per patient in 1 year. These data indicate that the lowest expected 1-year cost is associated with strategy C (maintenance H2RA) at $Can657 per patient, followed by intermittent PPI ($Can678), step-down maintenance H2RA ($Can748), step-down maintenance PA ($Can805), step-down maintenance PPI ($Can955) and maintenance PPI ($Can1093).

Although the maintenance PPI strategy had the highest expected cost, this strategy also had the lowest expected number of recurrences (0.20) and weeks with GORD (4.82) per patient in 1 year. Step-down maintenance PA had the next lowest expected number of recurrences (0.36), but had the highest expected weeks with GORD (12.60) because of the less effective and longer healing period with PA. Step-down maintenance PPI had about the same expected number of recurrences as maintenance PA (0.37) but ranked second lowest overall in terms of expected weeks with GORD (5.54). Intermittent PPI ranked worst in terms of expected recurrences (0.93), and the maintenance H_2RA strategies ranked between the strategies mentioned above for both recurrences and weeks with GORD.

The first task in comparing multiple strategies is to eliminate dominated strategies. As shown in figure 3, which plots the cost and outcome results relative to maintenance H_2RA (strategy C), a strategy would be dominated if an alternative lay to the southeast of it, having both better effectiveness and lower cost. Hence, step-down maintenance PA (strategy D) is dominated by 3 alternatives: maintenance H_2RA (strategy C), intermittent PPI (strategy A) and step-down maintenance H_2RA (strategy E). The next step is to identify the 'efficient frontier' of nondominated strategies. This frontier is illustrated in figure 3 as the line joining strategies C (origin), A, E and B. Any strategy that lies to the northwest of this frontier is considered dominated through principles of extended dominance. Hence, strategy F (step-down maintenance PPI) would be dominated because this level of effectiveness can be obtained at lower cost through a linear combination of strategies E and B.

The incremental cost effectiveness of the remaining strategies can now be calculated beginning with the least costly strategy (C) as the reference point and moving along the efficient frontier to determine the cost at which greater levels of effect can be purchased. As shown in table IX, the incremental cost effectiveness of intermittent PPI (A) is $Can8 per week free of GORD, step-down maintenance H_2RA (E) is higher at $Can44 and maintenance PPI (B) is higher still at $Can256.

Sensitivity Analyses

There were marked differences in expected costs, recurrences and weeks with GORD when using the lower and upper CIs for both healing and

Table VII. Gastro-oesophageal reflux disease (GORD) recurrence studies on maintenance therapy by drug class and dose size

Study	Dose	Period 0-6mo		Period 6-12mo	
		n	no. of recurrences (%)	n	no. of recurrences (%)
Bardhan et al.[85] (abs)	Placebo	133	96 (72)	37	12 (32)
Bate et al.[86]	Placebo	62	47 (76)	15	7 (47)
Blum et al.[87]	Placebo	113	37 (33)	76	21 (28)
Hegarty et al.[88]	Placebo	90	36 (40)	54	7 (13)
Hetzel et al.[77]	Placebo	107	88 (82)		
Laursen et al.[89]	Placebo	29	29 (100)		
Koelz et al.[90]	Placebo	33	14 (42)		
Robinson et al.[91]	Placebo	55	40 (73)	15	1 (7)
Sontag et al.[92] (abs)	Placebo	131	117 (89)		
Sontag et al.[93]	Placebo	47	39 (83)	8	0 (0)
Toussaint[94]	Placebo	43	18 (42)		
Placebo		**994**	**648 (65)**	**205**	**48 (23)**
Blum et al.[87]	CIS 10mg bid	125	28 (22)	97	15 (15)
Toussaint[94]	CIS 10mg bid	39	8 (21)		
Blum et al.[87]	CIS 20mg od	117	26 (22)	91	11 (12)
Vigneri et al.[95]	CIS 10mg tid	31	10 (32)	21	2 (10)
CIS 20-30mg		**312**	**72 (23)**	**209**	**28 (13)**
Koelz et al.[90]	R 150mg od	28	10 (36)		
Pace et al.[96]	R 150mg og	19	4 (21)	15	1 (7)
Dent et al.[97]	R 150mg bid	48	29 (60)	19	7 (37)
Hallerback et al.[98]	R 150mg bid	122	51 (42)	71	16 (23)
Hegarty et al.[88]	R 150mg bid	90	18 (20)	72	7 (10)
Lundell et al.[99]	R 150mg bid	16	11 (69)	5	3 (60)
Pace et al.[96]	R 300mg od	12	5 (42)	7	1 (14)
Vigneri et al.[95]	R 150mg tid	30	11 (37)	19	2 (11)
R 150-450mg		**365**	**139 (38)**	**208**	**37 (18)**
Bardhan et al.[85] (abs)	O 10mg od	130	38 (29)	92	10 (11)
Bate et al.[86]	O 10mg od	60	17 (28)	43	13 (30)
Hallerback et al.[98]	O 10mg od	123	34 (28)	89	13 (15)
Laursen et al.[89]	O 10mg od	64	42 (66)		
Zeitoun et al.[100] (abs)	O 10mg od	42	9 (21)		
Baldi et al.[101] (abs)	L 15mg od	295	50 (17)	245	30 (12)
Gough et al.[102]	L 15mg od	85	16 (19)	60	11 (18)
Robinson et al.[91]	L 15mg od	59	11 (19)	48	1 (2)
Sontag et al.[93]	L 15mg od	50	14 (28)	36	2 (6)
PPI-low dose		**908**	**231 (25)**	**613**	**80 (13)**
Baldi et al.[101] (abs)	O 20mg od	302	21 (7)	281	18 (6)
Bate et al.[86]	O 20mg od	68	10 (15)	58	8 (14)
Carling et al.[103] (abs)	O 20mg od	120	8 (7)	112	3 (3)
Dent et al.[97]	O 20mg od	46	4 (9)	39	1 (3)
Hallerback et al.[98]	O 20mg od	125	21 (17)	104	14 (13)
Laursen et al.[89]	O 20mg od	65	27 (42)		
Lundell et al.[99]	O 20mg od	34	8 (24)	26	3 (12)
Sontag et al.[92] (abs)	O 20mg od	138	41 (30)		
Vigneri et al.[95]	O 20mg od	33	1 (3)	32	4 (13)
Baldi et al.[101] (abs)	L 30mg od	309	15 (5)	294	28 (10)
Carling et al.[103] (abs)	L 30mg od	124	8 (6)	116	4 (3)
Gough et al.[102]	L 30mg od	72	10 (14)	56	5 (9)
Robinson et al.[91]	L 30mg od	56	4 (7)	52	1 (2)
Sontag et al.[93]	L 30mg od	49	14 (29)	35	5 (14)
PPI-regular dose		**1541**	**192 (12)**	**1205**	**94 (8)**

abs = abstract; **bid** = twice daily; **CIS** = cisapride; **L** = lansoprazole; **O** = omeprazole; **od** = once daily; **PPI** = proton pump inhibitor; **R** = ranitidine; **tid** = 3 times daily.

Table VIII. Recurrence probabilities by maintenance therapy drug regimen

Drug regimen	0-6mo recurrence			6-12mo recurrence		
	no. of pts at risk	n (%)	95% CI	no. of pts at risk	n	95% CI
Placebo	994	648 (65)	54, 77	205	48 (23)	14, 33
PA	312	72 (23)	18, 28	209	28 (13)	9, 18
H_2RA	365	139 (38)	28, 49	208	37 (18)	9, 27
PPI	1541	192 (12)	7, 18	1205	94 (8)	6, 10
PPI (low dose)	908	231 (25)	17, 34	613	80 (13)	8, 18

CI = confidence interval; **H_2RA** = H_2-receptor antagonist; **PA** = prokinetic agent; **PPI** = proton pump inhibitors; **pts** = patients.

recurrence rates. However, there were no changes in the relative ranking of strategies for either costs or outcomes. The basic conclusions of the base-case analysis were not altered by using the lower or upper 95% CIs for healing or recurrence rates.

Table X presents the results on expected cost based on alternative assumptions about the price of the H_2RA, the price of PPI and prescription dispensing fees. Priced at generic cimetidine (and assuming equivalent outcome as other H_2RAs), the maintenance H_2RA strategy is clearly the least costly strategy at $Can437 per patient per year. As shown in figure 4, when cimetidine prices are used, intermittent PPI (A) becomes dominated by step-down maintenance H_2RA (E), and step-down maintenance PPI (F) is dominated through extended dominance (i.e. a combination of strategies C, E and B is superior). Using cimetidine prices for H_2RA, the 'efficient frontier' of long term GORD management consists of strategies C, E and B.

In contrast, when brand name ranitidine (Zantac®) prices are used, the expected cost per patient per year for maintenance H_2RA would be the highest of all 6 strategies at $Can1122 for the year. The maintenance H_2RA strategy would become dominated by strategies A, B, E and F when Zantac® prices are used. Similarly, step-down maintenance H_2RA (strategy E), would also become dominated by the maintenance PPI strategies (B and F). Using Zantac® prices for H_2RA, the efficient frontier of long term GORD management consists of the 3 PPI-based strategies (i.e. intermittent PPI, step-down maintenance PPI and maintenance PPI).

Table IX. Base-case expected cost, recurrences, weeks with (without) gastro-oesophageal reflux disease (GORD) and incremental cost effectiveness

Strategy	Expected 1-year cost per patient ($Can)	Expected GORD recurrences per patient in 1y	Expected weeks with (without) GORD per patient in 1y	Incremental costs (ΔC) [$Can]	Incremental effects (ΔE) – GORD weeks averted	ΔC/ΔE ($Can/GORD week averted)
C: maintenance H_2RA	657	0.58	10.41 (41.59)			
A: intermittent PPI	678	0.93	7.78 (44.22)	21	2.63	8
E: step-down maintenance H_2RA	748	0.54	6.17 (45.83)	70[a]	1.61[a]	44[a]
B: maintenance PPI	1093	0.20	4.82 (47.18)	345[b]	1.35[b]	256[b]
D: step-down maintenance PA	805	0.36	12.60 (39.40)			Dominated by strategies A, C and E
F: step-down maintenance PPI	955	0.37	5.54 (46.46)			Dominated by extended dominance

a Relative to strategy A.

b Relative to strategy E.

H_2RA = H_2-receptor antagonist; **PA** = prokinetic agent; **PPI** = proton pump inhibitors; **$Can** = Canadian dollars.

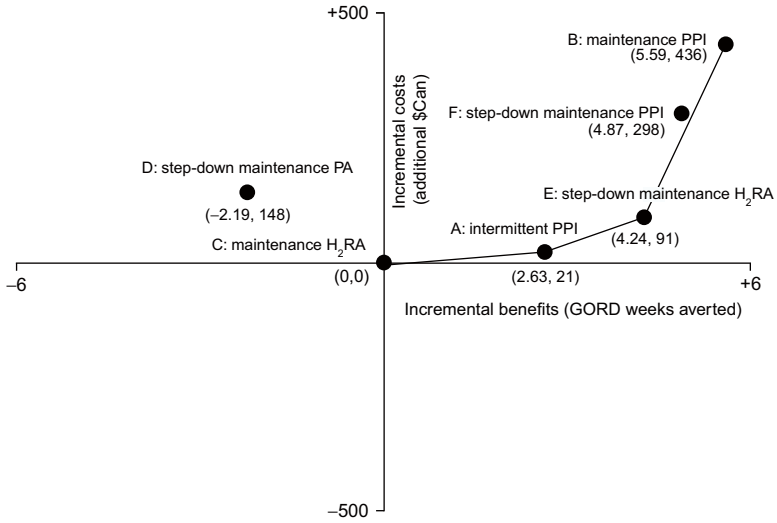

Fig. 3. Incremental costs and effects [weeks of gastro-oesophageal reflux disease (GORD) averted] relative to maintenance H_2RA. **H_2RA** = H_2-receptor antagonist; **PA** = prokinetic agent; **PPI** = proton pump inhibitors; **$Can** = Canadian dollars.

Finally, as shown in table X, the rank ordering of the cost results are not sensitive to alternative PPI costs (i.e. lansoprazole or pantoprazole) or Ontario average dispensing fees.

Discussion

Various techniques for data synthesis were used to summarise the available information on the costs and outcomes associated with 6 possible strategies for the long term management of patients with uncomplicated GORD of grades 2 to 4 (i.e. erosive oesophagitis). The 6 strategies were defined in terms of the therapeutic intent and embodied algorithms for switching to another drug if first-line therapy failed. Therefore, the evaluation was not of single drugs but of how such drugs are used in overall management strategies for the disease.

In our base-case analysis it was found that maintenance H_2RA was the least costly strategy, but second highest in terms of expected weeks with GORD

Table X. Sensitivity analysis by alternative drug prices and dispensing fees

Strategy	Base case	Expected 1-year cost per patient by variant ($Can)				
		variant #1: generic cimetidine for H_2RA	variant #2: brand Zantac® for H_2RA	variant #3: lansoprazole for PPI	variant #4: pantoprazole for PPI	variant #5: average Ontario dispensing fee
A: intermittent PPI	678	678	678	636	615	696
B: maintenance PPI	1093	1093	1093	1008	965	1128
C: maintenance H_2RA	657	437	1122	636	626	685
D: step-down maintenance PA	805	805	805	787	777	831
E: step-down maintenance H_2RA	748	584	1095	713	695	776
F: step-down maintenance PPI	955	955	955	986	943	991

H_2RA = H_2-receptor antagonist; **PA** = prokinetic agent; **PPI** = proton pump inhibitors; **$Can** = Canadian dollars.

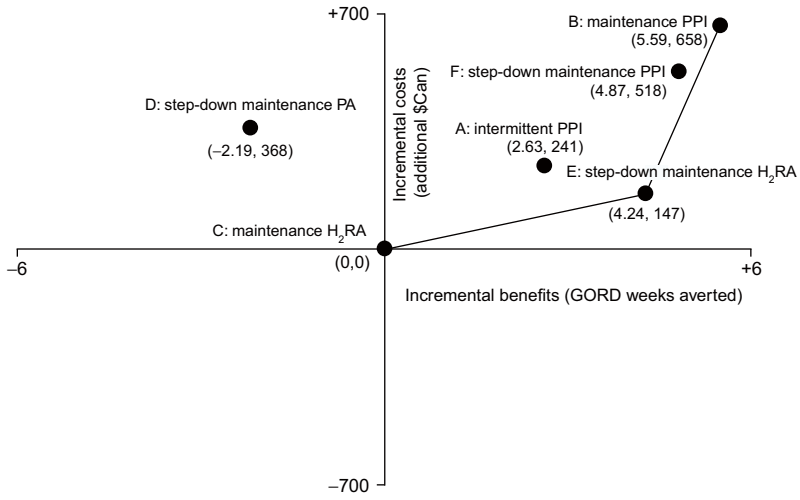

Fig. 4. Incremental costs and effects [weeks of gastro-oesophageal reflux disease (GORD)] averted relative to maintenance H_2RA using cimetidine prices for H_2RA. **H_2RA** = H_2-receptor antagonist; **PA** = prokinetic agent; **PPI** = proton pump inhibitors; **$Can** = Canadian dollars.

in 1 year. Step-down maintenance PA was dominated by 3 strategies and step-down maintenance PPI was dominated through principles of extended dominance by combinations of intermittent PPI, step-down maintenance H_2RA and maintenance PPI. The other 3 strategies (i.e. intermittent PPI, maintenance PPI and step-down maintenance H_2RA) all resulted in higher expected cost and fewer weeks with GORD compared with maintenance H_2RA. These strategies represent the 'efficient frontier' of long term GORD management in our base-case analysis. Using incremental analysis, we estimated that a move from maintenance H_2RA to intermittent PPI would cost $Can8 per additional week free of GORD, $Can44 per additional week free of GORD to then move to step-down maintenance H_2RA, and $Can256 per additional week free of GORD to move further to maintenance PPI.

It should be stressed that our analysis is a comparison of clinical strategies for management of erosive oesophagitis, and the labels we use for each strategy are merely an abbreviated form for the complex step-up, step-down and switching algorithms described in table I. Hence, 'intermittent PPI' (strategy A) is an initial attempt to use intermittent omeprazole but allows for a switch to higher dose PPI for those not healed and a switch to maintenance PPI for those who fail on the intermittent regimen. The results suggest that this graduated protocol for use of PPI has better patient outcomes than initiating treatment with maintenance H_2RA. In contrast, the early use of maintenance PPI (strategy B) or step-down maintenance H_2RA (strategy E) does yield fewer weeks with GORD but at a higher expected cost per patient. The analysis cannot resolve this cost-outcome trade-off; the value of moving to these clinically superior strategies is a judgement for decision-makers.

Previous cost-effectiveness studies have either found omeprazole to be dominant over H_2RA or have formulated misleading average cost-effectiveness ratios in their analysis. One of the key factors in the present study is that for the Canadian healthcare system, where 90% of prescriptions dispensed for ranitidine are generic, it makes sense to compare omeprazole strategies against generic ranitidine. Our sensitivity analysis in table X clearly indicates that, using the price of brand name ranitidine (Zantac®), then the maintenance H_2RA

and step-down maintenance H_2RA strategies become dominated by the maintenance PPI and step-down maintenance PPI strategies. Some previous US studies conclude that omeprazole therapy is dominant over ranitidine because at the time of these US-based studies, only the brand name ranitidine (Zantac®) was available (generic ranitidine became available in the US in July 1997). The price of H_2RA is a key factor influencing whether step-down maintenance PPI forms part of, or is contained within, the 'efficient frontier' for the long term management of GORD.

Similarly, if we are prepared to accept that cimetidine yields similar outcomes in GORD to ranitidine, then the price of generic cimetidine is sufficiently low that the intermittent PPI and step-down maintenance PPI strategies become unattractive alternatives through principles of dominance and extended dominance. At cimetidine prices, the 'efficient frontier' for the long term management of GORD consists of maintenance H_2RA, step-down maintenance H_2RA and maintenance PPI.

Conclusion

We attempted to model 6 different treatment strategies rather than single drugs and, in doing so, attempted to make the best use of available data on oesophagitis healing and recurrence. We found that the price of H_2RAs is an important factor in determining whether step-down maintenance PPI forms part of, or is contained within, the 'efficient frontier' of long term management for erosive oesophagitis.

Most studies of the management of patients with GORD are based on diagnostically confirmed oesophagitis healing and recurrence rates. More recent studies are attempting to use symptom-based scores as measures of treatment success and the need for additional therapy. The use of standardised symptom measures in clinical trials will permit the development of economic models that are based on symptomatology rather than endoscopic healing and recurrence. A model based on patient's symptoms will provide a better measure of treatment success for the patient (i.e. symptom-free days) and better reflect how patients will be managed outside of the clinical trial setting.

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