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Cost Effectiveness in Canada of a Multidrug Prepackaged Regimen (Hp-PAC®)† for *Helicobacter pylori* Eradication

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Abstract

Objective: To assess the cost effectiveness of a multidrug prepackaged regimen for *Helicobacter pylori*, the Hp-PAC® (lansoprazole 30mg, clarithromycin 500mg, amoxicillin 1g, all twice daily), relative to alternative pharmacological strategies in the management of confirmed duodenal ulcer over a 1-year period from 2 perspectives: (i) a strict healthcare payer perspective (Ontario Ministry of Health) excluding the patient copayment; and (ii) a healthcare payer perspective including the patient copayment.

Design: A decision-analytical model was developed to estimate expected per patient costs [1998 Canadian dollars ($Can)], weeks without ulcer and symptomatic ulcer recurrences for the Hp-PAC® compared with: proton pump inhibitor (PPI)-clarithromycin-amoxicillin (PPI-CA), PPI-clarithromycin-metronidazole (PPI-CM), PPI-amoxicillin-metronidazole (PPI-AM) and ranitidine-bismuth-metronidazole-tetracycline (RAN-BMT).

Main outcome measures and results: All PPI-based regimens had higher expected costs but better outcomes relative to RAN-BMT. From a strict healthcare payer perspective, PPI-CM ($Can209) yielded lower expected costs than PPI-CA ($Can221) and slightly lower costs than Hp-PAC® ($Can211). However, these 3 regimens all shared identical outcomes (51.2 weeks without ulcer). When the current Ontario, Canada, $Can2 patient copayment was added to the dispensing fee, Hp-PAC® yielded lower costs ($Can214) than PPI-CM ($Can216).

Conclusion: From a strict healthcare payer perspective, Hp-PAC® is weakly dominated by PPI-CM with an incremental cost effectiveness (relative to RAN-BMT) of $Can5.77 per ulcer week averted. When the patient copayment is added to this perspective, Hp-PAC® weakly dominates PPI-CM ($Can5 per ulcer week averted). Regardless of perspective, Hp-PAC® and PPI-CM differed by only $Can2 per patient over 1 year and the expected time without ulcer was 51.2 weeks for both. More data on the clinical and statistical differences in *H. pylori* eradication with Hp-PAC® and PPI-CM would be useful. This analysis does not in-

† Use of tradenames is for product identification only and does not imply endorsement.

clude the possible advantage of Hp-PAC® in terms of compliance and antibacterial resistance.

Helicobacter pylori is recognised as a major contributor to the development of duodenal ulcer. A 1994 US National Institutes of Health (NIH) consensus conference noted that '. . . nearly all patients with duodenal ulcer have *H. pylori*', and that the association with gastric ulcer is '. . . only slightly less strong'.[1] The NIH panel recommended treatment with antimicrobial agents for patients with peptic ulcer disease with *H. pylori* in addition to antisecretory drugs whether on first presentation with the illness or on recurrence.

Recent Canadian consensus guidelines emphasise the need for *H. pylori* eradication and suggest proton pump inhibitor (PPI)-clarithromycin-amoxicillin (PPI-CA) and PPI-clarithromycin-metronidazole (PPI-CM) as first-line eradication regimens because of their high eradication rates (≥80%).[2]

A number of economic evaluations have been conducted since the NIH consensus conference. O'Brien et al.[3] structured the economic problem as a comparison between 3 global treatment strategies: (i) intermittent acid suppression [H_2 receptor antagonist (H_2RA) or PPI]; (ii) maintenance acid suppression (H_2RA); or (iii) *H. pylori* eradication with an H_2RA and bismuth triple therapy or with omeprazole plus amoxicillin or clarithromycin. Eradication strategies were less costly and more effective (fewer symptomatic recurrences) than the other 2 strategies; however, because of limited studies at the time, they could not conclude which of the *H. pylori* regimens offered best value for money.

In a subsequent evaluation for the Canadian Coordinating Office of Health Technology Assessment (CCOHTA), O'Brien et al.[4,5] confirmed that eradication strategies were dominant over intermittent or maintenance acid suppression. Among the *H. pylori* eradication strategies, triple therapy with omeprazole and metronidazole and either clarithromycin or amoxicillin offered the best value for money over bismuth triple therapy.

In a recent economic evaluation, Taylor et al.[6] found bismuth triple therapy and triple therapies containing PPIs to be associated with the lowest rate of ulcer recurrence and cost. Although Taylor and colleagues focused on recent clinical data and new eradication regimens, there were limitations with the analysis. First, efficacy rates were adjusted using 1987 compliance data from a nonsteroidal anti-inflammatory drug study. Secondly, ulcer rates were not adjusted for 'symptomatic' recurrence. Hence, the recurrence rates may be an overestimate of what would be observed in clinical practice. Finally, data from all PPIs were combined without first assessing if they produce the same rates of healing.

Recently, the Canadian Therapeutic Products Directorate approved a pre-packaged PPI-containing triple regimen called the Hp-PAC® (lansoprazole 30mg, clarithromycin 500mg, amoxicillin 1g, all twice daily). An economic advantage of the Hp-PAC® is that it will be dispensed as a single prescription attracting one dispensing fee. Traditionally, the individual medications would be dispensed as separate prescriptions each with a dispensing fee.

Therefore, the objective of this study is to compare the expected costs and outcomes of the Hp-PAC® relative to currently used PPI-based regimens and ranitidine-bismuth-metronidazole-tetracycline (RAN-BMT) from 2 perspectives: (i) a strict healthcare payer perspective [Ontario Ministry of Health (MOH)] excluding the patient copayment, hereafter referred to as MOH+; and (ii) a healthcare payer perspective including the patient copayment, hereafter referred to as MOH–. Considering both perspectives is especially important for this problem because a traditional 3-drug regimen for *H. pylori* would require a patient in Ontario, Canada, to pay 3 copayments of 2 Canadian dollars ($Can) for each drug.

Given that the active ingredients of Hp-PAC® are the same as PPI-CA, a secondary objective of the study was to determine the economic impact of

multiple drug pre-packaging on drug and dispensing costs. Therefore, we attempt to answer the question: how will the perspective of a cost-effectiveness analysis affect the rank ordering of the Hp-PAC® relative to other *H. pylori* eradication regimens?

Methods

Overview of Analytical Approach

The analytical approach was divided into 3 key components. First, the therapeutic decision problem was structured using the principles of clinical decision analysis where clinical events and costs are structured as a decision tree. Secondly, expected costs and outcomes were calculated by determining the probabilities of relevant clinical events (i.e. ulcer healing rates, *H. pylori* eradication rates, ulcer recurrence rates) using principles of data synthesis from reviewed literature. Search criteria were identified and used for retrieval and subsequent pooling of relevant rates from published studies for inclusion in the model. Thirdly, principles of cost-effectiveness analysis were used for comparing treatment strategies in terms of weak and strong dominance and incremental cost effectiveness. Sensitivity analysis was used to explore key areas of uncertainty.

Decision-Analysis Model

Our model was based on a Markov process with a cycle length of approximately 3 months (exactly 91 days). A Markov model is a recursive process that is useful for clinical situations where patients have an ongoing risk of experiencing a defined set of events.[7] The timing of these events may be uncertain and the event may occur more than once. A 3-month Markov cycle model allows for the possibility of more than 2 ulcer relapses per year. Three months represents a reasonable period of time over which relapses can be observed.

The model commences with a cohort of patients with confirmed, uncomplicated duodenal ulcer initially receiving 'heal-and-eradicate' therapy with 1 of the 5 treatment strategies under study as outlined in table I. If patients are unhealed following a PPI-based eradication regimen, we assumed that they receive 2 weeks of a PPI (administered on a twice daily regimen). If they remain unhealed at 4 weeks, they receive another 2 weeks of PPI monotherapy. At 6 weeks, we assumed all patients are healed. If patients are unhealed following RAN-BMT (where ranitidine is given for 4 weeks), we assumed they receive another 4 weeks of ranitidine at which point we assumed 100% healing. The probability of ulcer relapse in subsequent 3 month cycles is dependent upon whether *H. pylori* was successfully eradicated by the treatment regimen.

If patients relapse, we assumed they will be treated with a different drug regimen. Patients first treated with PPI-amoxicillin-metronidazole (PPI-AM), PPI-CM and RAN-BMT strategies are assumed to be switched to Hp-PAC® upon recurrence. Patients first treated with PPI-CA and Hp-PAC® are assumed to be switched to PPI-CM treatment upon recurrence. For second and third relapses, we assumed patients will be treated with a PPI to heal followed by maintenance PPI therapy.

Clinical and Cost Outcome Measures

Our primary clinical outcome is 'time free from ulcer' over the 12-month period of the model. This outcome measure incorporates both the speed with which an ulcer is healed and the likelihood of an ulcer recurrence. The expected costs for each strategy include both initial drug therapy and 'downstream' costs due to management of ulcer recurrence in the 1-year interval. The model does not assume additional diagnostic testing for the presence of *H. pylori* or testing to confirm eradication.

Key Clinical Model Inputs

There were 3 key clinical inputs into the decision model: time with ulcer per healing episode; *H. pylori* eradication rates for each strategy; and the probability of ulcer recurrence. These parameters are discussed in the following sections. All costs are expressed in 1998 Canadian dollars ($Can) [$US1 = $Can1.48].

Table I. Costs of drug regimens, excluding dispensing fee

Regimen	Dose	Days of therapy (from-to)	Cost ($Can per drug)[a,b]	Cost ($Can per regimen)
PPI-AM				
Average PPI[c]		1-7	31.36	
Amoxicillin	[500mg × 2] bid	1-7	6.16	
Metronidazole	[250mg × 2] bid	1-7	0.84	38.36
PPI-AM (omeprazole as PPI)	20mg bid	1-7	33.88	40.68
PPI-AM (lansoprazole as PPI)	30mg bid	1-7	30.80	37.80
PPI-AM (pantoprazole as PPI)	40mg bid	1-7	29.26	36.26
PPI-CA				
Average PPI[c]		1-7	31.36	
Clarithromycin	500mg bid	1-7	45.50	
Amoxicillin	[500mg × 2] bid	1-7	6.16	83.02
PPI-CA (omeprazole as PPI)	20mg bid	1-7	33.88	85.54
PPI-CA (lansoprazole as PPI)	30mg bid	1-7	30.80	82.46
PPI-CA (pantoprazole as PPI)	40mg bid	1-7	29.26	80.09
PPI-CM				
Average PPI[c]		1-7	31.36	
Clarithromycin	500mg bid	1-7	45.50	
Metronidazole	[250mg × 2] bid	1-7	0.84	77.70
PPI-CM (omeprazole as PPI)	20mg bid	1-7	33.88	80.22
PPI-CM (lansoprazole as PPI)	30mg bid	1-7	30.80	77.14
PPI-CM (pantoprazole as PPI)	40mg bid	1-7	29.26	75.74
RAN-BMT				
Ranitidine	150mg bid	1-28	24.64	
Bismuth[d]	2 tablets qid	1-14	16.80	
Metronidazole	250mg qid	1-14	1.68	
Tetracycline	[250mg × 2] qid	1-14	2.24	45.36
Hp-PAC®				
Lansoprazole	30mg bid	1-7		
Clarithromycin	500mg bid	1-7		
Amoxicillin	[500mg × 2] bid	1-7		80.96
Maintenance PPI				
Average PPI[c]		1-91	203.84	203.84

a Unit price sources: all Ontario Drug Benefit prices (1998), except bismuth (survey of local pharmacies) and clarithromycin 500mg (manufacturers price with 10% pharmacy mark-up), all with mark-up.

b Unit prices (all with 10% mark-up excluding dispensing fees): ranitidine (generic) 150mg, $Can0.44; omeprazole 20mg, $Can2.42; lansoprazole 30mg, $Can2.20; pantoprazole 40mg, $Can2.09; Pepto-Bismol® tablets, $Can0.15; amoxicillin (generic) 500mg, $Can0.22; clarithromycin 500mg, $Can3.25; metronidazole (generic) 250mg, $Can0.03; tetracycline 250mg, $Can0.02.

c Omeprazole 20mg, lansoprazole 30mg, pantoprazole 40mg.

d Pepto-Bismol® contains 262mg bismuth subsalicylate and 350mg calcium carbonate; 2 tablets of bismuth suggested in recent publications.[8]

bid = twice daily; **Hp-PAC®** = lansoprazole-clarithromycin-amoxicillin, prepackaged; **PPI** = proton pump inhibitor; **PPI-AM** = PPI-amoxicillin-metronidazole; **PPI-CA** = PPI-clarithromycin-amoxicillin; **PPI-CM** = PPI-clarithromycin-metronidazole; **qid** = 4 times daily; **RAN-BMT** = ranitidine-bismuth-metronidazole-tetracycline; **$Can** = Canadian dollars.

Time with Ulcer per Healing Episode

Using random effects meta-analysis techniques,[9-11] the probability of healing was estimated at different time points using pooled data from published studies. In all PPI-based ulcer healing studies, all patients had endoscopically diagnosed duodenal ulcer at baseline. *H. pylori* positivity was assessed by at least 1 method in the PPI plus 1 antibacterial and PPI plus 2 antibacterial studies. Studies for PPI-based treatments were primarily identified from Medline (1985 to May 1997) and a previous economic analysis.[4] Ranitidine healing data were estimated from an earlier analysis.[4]

Helicobacter pylori Eradication Probabilities

For PPI-based regimens, no published meta-analysis on eradication rates was available that summarised all regimens of interest in the duodenal ulcer patient population. Therefore, we estimated the eradication rates based on data provided in a recent preliminary report[12] and a threshold value provided from the Canadian *H. pylori* consensus conference.[2] For RAN-BMT, we utilised an earlier randomised controlled trial[13] and meta-analysis.[14]

Ulcer Recurrence Probabilities

Studies reporting ulcer recurrence rates based on *H. pylori* status were identified and analysed using literature sources similar to those for the healing analysis [Medline (1992 to 1997) and a previous economic analysis[4]]. Recurrence rates were adjusted to account for the fact that approximately 76% of endoscopically diagnosed ulcer recurrences[4] are symptomatic, resulting in a physician visit.

Key Cost Model Inputs

In the decision model, costs are incurred for: (i) drug therapy for the initial duodenal episode; and (ii) the management of recurrent duodenal ulcers.

Cost of Treating Duodenal Ulcer Episodes

The primary source of drug price information was the Best Available Price from the Ontario Drug Benefit (ODB) Formulary with a 10% pharmacy mark-up. For drugs not listed on the formulary, either the manufacturer's price with a 10% mark-up was used (for clarithromycin 500mg) or a small survey of local pharmacies was conducted (for Pepto-Bismol®). Regimen costs (with the 10% mark-up) are presented in table I along with variations for sensitivity analyses in the regimen costs when different PPIs are used in PPI-AM, PPI-CA and PPI-CM. The PPI cost used in PPI-AM, PPI-CA and PPI-CM, and maintenance PPI therapy was a simple average of the 3 PPIs (omeprazole, lansoprazole, pantoprazole).

In Ontario, pharmacies dispensing an ODB eligible prescription are entitled to a $Can6.11 dispensing fee. A portion of this fee, $Can4.11, is paid by the ODB programme directly to the pharmacy. The patient pays the balance of the fee, the $Can2.00 copayment. For the MOH+ perspective, a dispensing fee of $Can4.11 was used ($Can6.11 ODB fee minus $Can2.00 patient copayment). For the MOH– perspective, patients pay a $Can2.00 copayment (total $Can6.11). Other out-of-pocket costs, such as over-the-counter antacids, were not included but there is no reason to suppose these costs would vary between regimens. Only dispensing fees and copayments set by the MOH are considered in this analysis. Across Canada, dispensing fees and copayments vary widely depending on the type of payer (i.e. public, private or cash-paying patient).

The Hp-PAC® cost was determined from the manufacturer to be $Can73.60 ($Can80.96 incorporating the 10% pharmacy mark-up). From the MOH+ perspective, the Hp-PAC® attracts one dispensing fee ($Can4.11), and therefore its total cost is $Can85.07 ($Can9.72 less than the individually dispensed drugs each with a dispensing fee). From the MOH– perspective, a $Can6.11 fee is charged ($Can4.11 paid by the MOH and $Can2 by the patient), and therefore its total cost is $Can87.07.

Cost of Managing Duodenal Ulcer Recurrences

Resource use data associated with the management of symptomatic ulcer recurrences were derived from a previous expert physician panel (4 gastroenterologists, 2 family doctors),[4] where a

modified Delphi technique[15] was used to estimate the percentage likelihood and volume of various services used when patients present with ulcer recurrence symptoms.

In this analysis, we have used the physician panel's recommendations with the exception of gastroenterologist visits in an attempt to reflect changes in the management of *H. pylori*. Originally, 1 gastroenterologist reassessment and 2 gastroenterologist partial assessments were assumed for each recurrence. For this analysis, we assumed the general practitioner (GP) will conduct the follow-up and thus have removed the gastroenterologist partial assessments. A GP minor assessment is now assumed if patients are unhealed following *H. pylori* eradication therapy.

Costs (combined hospital and physician service cost) for procedures such as upper gastrointestinal endoscopy were estimated from 2 sources: (i) an Ontario Case Costing Project hospital in South-Western Ontario; and (ii) the physician fee schedule for Ontario,[16] which itemises allowable physician reimbursement by procedure under the provincial health insurance plan. These unit costs, physician fees and utilisation estimates by recurrence are provided in table II.

Sensitivity Analyses

To assess the impact of uncertainty surrounding many of the data estimates, sensitivity analyses were conducted on the: (i) PPI-AM eradication rate; (ii) eradication rate of PPI-CM versus PPI-CA to simulate metronidazole and/or clarithromycin resistance; (iii) cost of omeprazole, lansoprazole and pantoprazole in the PPI-based regimens; and (iv) effect of increasing the dispensing fee.

Results

Clinical Model Input Results

Ulcer Healing Probabilities and Time-with-Ulcer per Healing Episode

The proportion of patients healed at various time points for PPI alone, PPI plus 1 antibacterial, PPI plus 2 antibacterials and ranitidine-based regimens are provided in table III and figure 1. From these data, 3 separate healing curves were estimated with simple linear interpolation between time points. The time-with-ulcer per healing episode was calculated as the area above each curve. The time-with-ulcer per healing episode was applied to duodenal ulcer episodes treated with PPI plus 2 antibacterial regimens, whereas the time-with-ulcer for PPI alone was applied to duodenal

Table II. Healthcare utilisation and costs of managing ulcer recurrence (excluding drugs)[a]

Cost component	Unit cost ($Can)	First recurrence		Second and subsequent recurrences	
		%	cost ($Can)	%	cost ($Can)
Visits to gastroenterologist					
Gastroenterologist reassessment	38.65	1[b]	38.65	1[b]	38.65
Tests and procedures					
Abdominal ultrasound (complete)	99.61	0		2	2.00
Gastric biopsy	325.00	95	308.75	95	308.75
Complete blood count	9.21	50	4.61	50	4.61
Culture (*Helicobacter pylori*)	46.69	0		50	23.35
Serum gastrin	7.72	0		5	0.39
Upper gastrointestinal endoscopy	118.22	95	112.31	95	112.31
Urea ($Can5.98) + electrolytes ($Can14.24)	20.22	25	5.06	40	8.09
Cost per recurrence			**469.38**		**498.15**

a Modified from the Canadian Coordinating Office of Health Technology Assessment (CCOHTA) report.[4]

b Number of visits.

$Can = Canadian dollars.

Table III. Cumulative probability of ulcer healing by weeks on therapy

Regimen	1 Week		2 Weeks		4 Weeks		8 Weeks	
	number of study arms	probability healed (95% CI)	number of study arms	probability healed (95% CI)	number of study arms	probability healed (95% CI)	number of study arms	probability healed (95% CI)
PPI alone			43	0.64 (0.61, 0.68)	55	0.89[a] (0.87, 0.90)		
PPI plus 1 antibacterial[b,c]			16	0.81 (0.75, 0.86)	12	0.92 (0.90, 0.95)		
PPI plus 2 antibacterials[c,d]	11	0.92 (0.88, 0.95)	7	0.94 (0.90, 0.98)	14	0.96[e] (0.94, 0.98)		
Ranitidine					26	0.74 (0.69, 0.78)	25	0.88[f] (0.85, 0.91)

a Area-above-the-curve for 4 weeks of PPI alone = 1.83 weeks with ulcer.

b PPI plus amoxicillin and PPI plus clarithromycin studies found. Studies analysed together.

c Due to large variations in antibacterial dose and duration, all doses analysed together.

d All antibacterial types analysed together.

e Area-above-the-curve for 4 weeks of a PPI plus 2 antibacterials = 0.71 weeks with ulcer.

f Area-above-the-curve for 8 weeks of ranitidine = 3.30 weeks with ulcer.

CI = confidence interval; **PPI** = proton pump inhibitor.

ulcer episodes treated with a maintenance PPI regimen.

Area-above-the-curve calculations for 4 weeks of a PPI alone resulted in 1.83 weeks with ulcer. Similarly, 4 weeks of a PPI plus 2 antibacterials and 8 weeks of ranitidine resulted in 0.71 and 3.30 weeks with ulcer, respectively.

H. pylori Eradication Probabilities

For PPI-based regimens, the following eradication rates were used in the model: PPI-AM 71%, PPI-CA 88% and PPI-CM 90%. The PPI-CA and PPI-CM rates were consistent with those reported by Huang et al.,[12] who examined *H. pylori* eradication rates in patients with duodenal ulcer, gastric ulcer and non-ulcer dyspepsia. These rates are broadly consistent with the threshold rates reported in the Canadian *H. pylori* consensus conference (i.e. PPI-CA and PPI-CM are reported to have greater than 80% eradication rates on an intention-to-treat basis).[2] For RAN-BMT, 86% was used as the base case from the meta-analysis by Penston[14] (BMT for 2 weeks of therapy).

Ulcer Recurrence Probabilities

In *H. pylori*–negative patients, the ulcer recurrence rate at 6 months was 3.0% [95% confidence interval (CI) 1.0, 5.0; 19 study arms] and at 12 months was 2.0% (95% CI 1.0, 3.0; 28 arms). The 12-month ulcer recurrence rate may have been lower than the 6-month rate because of more studies reporting 12-month data. Therefore, in the model we assumed 2.5% as the 12-month duodenal ulcer recurrence rate (the average between the 6- and 12-month values). In *H. pylori*–positive patients the 6-month recurrence rate was 52% (95% CI 35, 69; 20 arms) and the 12-month recurrence rate was 62% (95% CI 45, 80; 21 arms).

For maintenance PPI therapy, we assumed that the ulcer recurrence rate would approximate that of the *H. pylori*–negative rate because the patient is likely to be *H. pylori*–negative following 2 *H. pylori* eradication regimens and maintenance PPI therapy. All recurrence rates were adjusted by a factor of 0.76 to approximate symptomatic ulcer recurrences.

Cost-Effectiveness Results

In table IV, we present both the MOH+ and MOH– perspectives of our analysis. Our base case is the MOH+ perspective. For each of the 5 strategies we present expected 1-year costs per patient, symp-

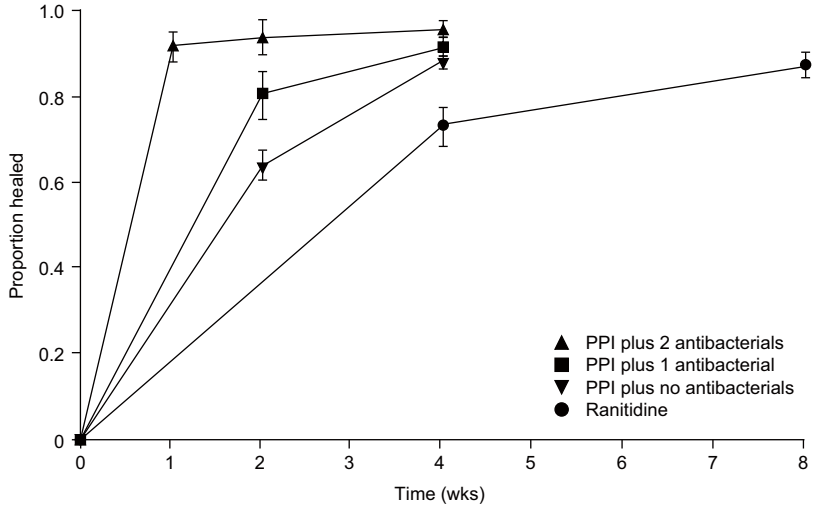

Fig. 1. Healing time curves for ranitidine and proton pump inhibitor (PPI)-based regimens (95% confidence interval).

tomatic ulcer recurrences per 100 patients and expected weeks per patient without ulcer in 1 year.

The rate of symptomatic ulcer recurrence per 100 patients is lowest for the PPI-CM regimen (7.3 per 100) followed by PPI-CA (8.2) and Hp-PAC® (8.2), RAN-BMT (9.4) and PPI-AM (17.2). The rank-ordering of regimens according to recurrence is consistent with prior expectation given the eradication rates used in the model with PPI-CM having the highest eradication rate at 90% and PPI-CA and the Hp-PAC® sharing the same eradication rate. The expected weeks per patient without ulcer were equivalent at 51.2 weeks for PPI-CM, PPI-CA and Hp-PAC® and were lower for PPI-AM (51.1 weeks) and for RAN-BMT (48.6 weeks).

From an MOH+ perspective, the expected cost per patient over 1 year was highest for PPI-AM ($Can234) followed by PPI-CA ($Can221), Hp-PAC® ($Can211), PPI-CM ($Can209) and RAN-BMT ($Can194).

The relationships between costs and outcomes are presented in table IV and the cost and effect coordinates are plotted in figure 2, with RAN-BMT used as the reference point. From an MOH+ perspective, the PPI-based regimens have higher expected costs with better outcomes relative to RAN-BMT. Among the PPI regimens, PPI-AM is strongly dominated (having higher costs and lower benefits than an alternative). PPI-CM yields lower expected costs than PPI-CA ($Can12) and slightly lower costs than Hp-PAC® ($Can2) over a 1-year period. However, these 3 regimens have identical outcomes, and therefore Hp-PAC® and PPI-CA are only weakly dominated (i.e. higher cost with same outcome as alternative).

Following accepted conventions for comparing mutually exclusive strategies,[17] these dominated alternatives are not considered further in the incremental analysis and an efficiency frontier is the locus of nondominated alternatives in the incremental cost, incremental effectiveness (ΔC, ΔE) space relative to RAN-BMT as the origin. From the MOH+ perspective, PPI-CM is the only nondominated alternative on this locus. PPI-CM yields an incremental cost-effectiveness ratio of $Can5.77 per ulcer week averted relative to RAN-BMT.

From the MOH– perspective, the $Can2 copayment is added to the dispensing fee as an out-of-pocket expense. Outcomes remain the same but the expected cost per patient over 1 year changes: PPI-AM ($Can240), PPI-CA ($Can228), PPI-CM ($Can216), Hp-PAC® ($Can214) and RAN-BMT

($Can201). The rank ordering (by cost) of Hp-PAC® and PPI-CM change as the expected cost of Hp-PAC® becomes $Can2 lower than for PPI-CM. Hp-PAC® yields an incremental cost-effectiveness ratio of $Can5.00 per ulcer week averted relative to RAN-BMT.

In summary, RAN-BMT remains the least costly and least effective strategy from both perspectives. However, the choice of perspective determines which strategy is the next nondominated but more costly and more effective strategy that should be considered if a decision-maker is willing to pay more for greater outcomes (i.e. the relevant mutually exclusive alternative for calculation of an incremental cost-effectiveness ratio). From an MOH+ perspective, PPI-CM is the only strategy on the efficiency frontier with an incremental cost effectiveness of $Can5.77 per ulcer-week averted (fig. 2a). Both PPI-CA and Hp-PAC® are weakly dominated by PPI-CM (having same effects and higher costs), and PPI-AM is strongly dominated (having lower effects and higher costs).

If the $Can2 copayment is included (MOH– perspective), Hp-PAC® becomes the only nondominated alternative on the efficiency frontier with an incremental cost effectiveness of $Can5 per ulcer-week averted (fig. 2b).

Sensitivity Analyses

We conducted 4 main sensitivity analyses. We varied the: (i) PPI-AM eradication rate; (ii) eradication rate of PPI-CM versus PPI-CA to simulate metronidazole and/or clarithromycin resistance; (iii) omeprazole, lansoprazole and pantoprazole costs in the PPI-based regimens; and (iv) the dispensing fee.

We found that PPI-AM eradication rates range considerably in the literature. The draft duodenal ulcer guidelines from Holbrook et al.[18] (being produced for the MOH) suggest a 77% eradication rate for PPI-AM. Changing the PPI-AM eradication rate to 77% lowers the expected cost for this strategy. However, PPI-AM is still dominated by PPI-CM and Hp-PAC®.

The eradication rate of PPI-CM was varied to assess the impact of metronidazole and/or clarithromycin resistance on the cost effectiveness of PPI-CM relative to Hp-PAC®. When the eradica-

Table IV. Expected costs, ulcer recurrences and incremental cost effectiveness using weeks without ulcer over 1 year

Strategy	Expected cost per patient ($Can)	Symptomatic ulcer recurrences per 100 patients	Expected weeks[a] without ulcer	ΔC ($Can)	ΔE (ulcer weeks averted)	ΔC/ΔE ($Can/ulcer week averted)
MOH+ perspective (base case)						
RAN-BMT	194	9.4	48.6	–	–	–
PPI-CM	209	7.3	51.2	15	2.6	5.77
Hp-PAC®	211	8.2	51.2			Weakly dominated
PPI-CA	221	8.2	51.2			Weakly dominated
PPI-AM	234	17.2	51.1			Strongly dominated
MOH– perspective						
RAN-BMT	201	9.4	48.6	–	–	–
Hp-PAC®	214	8.2	51.2	13	2.6	5.00
PPI-CM	216	7.3	51.2			Weakly dominated
PPI-CA	228	8.2	51.2			Weakly dominated
PPI-AM	240	17.2	51.1			Strongly dominated

a Rounded to the first decimal place.

CI = confidence interval; **Hp-PAC®** = lansoprazole-clarithromycin-amoxicillin, prepackaged; **MOH+** = Ontario Ministry of Health perspective excluding the patient copayment; **MOH–** = MOH perspective including the patient copayment; **PPI** = proton pump inhibitor; **PPI-AM** = PPI-amoxicillin-metronidazole; **PPI-CA** = PPI-clarithromycin-amoxicillin; **PPI-CM** = PPI-clarithromycin-metronidazole; **RAN-BMT** = ranitidine-bismuth-metronidazole-tetracycline; **$Can** = Canadian dollars; **ΔC** = incremental cost; **ΔC/ΔE** = incremental cost-effectiveness ratio; **ΔE** = incremental effectiveness.

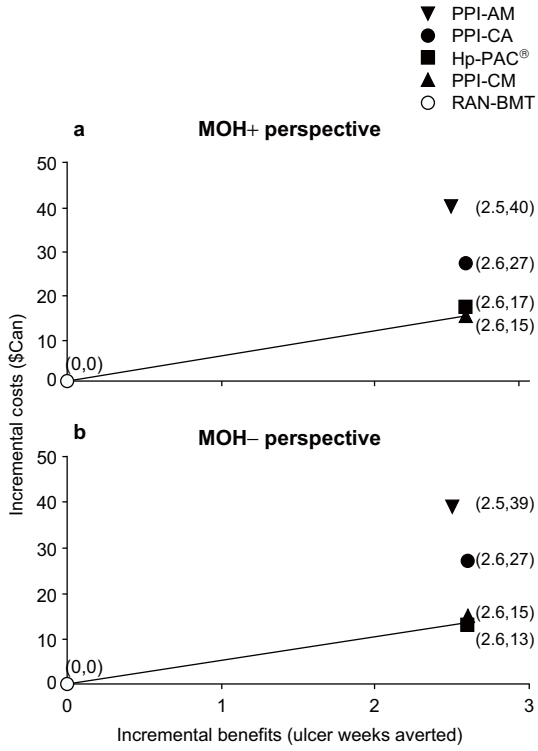

Fig. 2. Incremental cost-effectiveness (CE) relationships between the 5 treatment regimens. (**a**) MOH+ perspective: CE ratio (PPI-CM *vs* RAN-BMT) = 5.77; (**b**) MOH– perspective: CE ratio (Hp-PAC® *vs* RAN-BMT) = 5.00. **Hp-PAC®** = lansoprazole-clarithromycin-amoxicillin, prepackaged; **MOH+** = Ontario Ministry of Health perspective excluding the patient copayment; **MOH–** = MOH perspective including the patient copayment; **PPI** = proton pump inhibitor; **PPI-AM** = PPI-amoxicillin-metronidazole; **PPI-CA** = PPI-clarithromycin-amoxicillin; **PPI-CM** = PPI-clarithromycin-metronidazole; **RAN-BMT** = ranitidine-bismuth-metronidazole-tetracycline; **$Can** = Canadian dollars.It should be noted that the impact of metronidazole and/or clarithromycin resistance on eradication rates is difficult to estimate. A contributing issue is the fact that a proportion of patients with resistant organisms were probably included in the clinical trials from which our base-case eradication rates are derived.

tion rate of PPI-CM decreases, the expected costs of PPI-CM increase. Therefore, Hp-PAC® becomes attractive relative to PPI-CM with respect to costs. If the eradication rate of PPI-CM is lower than 88% (threshold value), Hp-PAC® also becomes both more effective and less costly than PPI-CM.

In table V, we test the sensitivity of the results to the individual PPI costs (in all areas of the model except Hp-PAC®). For example, if omeprazole is substituted as the PPI, it is used in the PPI-AM, PPI-CA and the PPI-CM regimens. It is also used as the PPI in the switch therapies and in the PPI maintenance therapy for all regimens. This is why the expected costs of the Hp-PAC® arm change (i.e. lansoprazole is always the PPI in this regimen, but the PPI in the switch therapy and maintenance PPI therapy will change within this arm).

In our base case, the PPI cost was a simple average of the 3 PPIs available on the Canadian market. The average cost of the 3 PPIs was compared with the Hp-PAC® in which the cost of lansoprazole is used (pre-packaged with lansoprazole). When the individual PPI cost for omeprazole is used, the rank order of PPI-CM and Hp-PAC® are identical. With omeprazole, the expected costs for Hp-PAC® and PPI-CM are both $Can212. With pantoprazole, the expected costs of Hp-PAC® are $Can210 and for PPI-CM are $Can207. The cost rank ordering of PPI-CM and Hp-PAC® does vary with respect to the assumed PPI acquisition cost, but this variation is small (±$Can2) with respect to the overall 1-year cost per patient.

In figure 3, we display the effect of increasing the dispensing fee per item on the expected costs of PPI-CM, PPI-CA and Hp-PAC® while holding the patient copayment constant at zero (i.e. MOH+ perspective). As anticipated, the expected costs for all regimens increases linearly with the dispensing fee, but the cost *difference* between PPI-CM and PPI-CA is invariant to the increase in dispensing fee. A threshold dispensing fee of $Can4.92 would make the expected costs of Hp-PAC® and PPI-CM equal. Even at a dispensing fee of zero, the PPI-CA regimen is more costly than Hp-PAC®.

Discussion

In this analysis, we have built upon the earlier work by O'Brien et al.[4] to compare the new Hp-PAC® with existing PPI-based regimens and RAN-BMT. Two perspectives were examined: (i) a strict healthcare payer perspective excluding the patient copayment (MOH+); and (ii) a healthcare payer perspective including the patient copayment (MOH–).

Table V. Sensitivity analyses on expected 1-year cost per patient by alternative PPI prices, MOH+ perspective

Regimen[a]	Expected cost per patient for 1 year ($Can)			
	base case (average PPI price)	omeprazole price	lansoprazole price	pantoprazole price
RAN-BMT	194	194	194	194
PPI-CM	209	212	209	207
Hp-PAC®	211	212	211	210
PPI-CA	221	225	220	218
PPI-AM	234	237	233	231

a Lansoprazole remains the PPI in the Hp-PAC®. The PPI changes in the PPI-AM regimen, PPI-CA regimen and the PPI-CM regimen. The PPI also changes in the PPI switch therapies and in the PPI maintenance therapy for all branches (HP_1-HP_5).

Hp-PAC® = lansoprazole-clarithromycin-amoxicillin, prepackaged; **MOH+** = Ontario Ministry of Health perspective excluding the patient copayment; **PPI** = proton pump inhibitor; **PPI-AM** = PPI-amoxicillin-metronidazole; **PPI-CA** = PPI-clarithromycin-amoxicillin; **PPI-CM** = PPI-clarithromycin-metronidazole; **RAN-BMT** = ranitidine-bismuth-metronidazole-tetracycline; **$Can** = Canadian dollars.

The packaging of 3 separate chemical entities in Hp-PAC® under one Drug Identification Number presents a unique opportunity to assess the impact of drug packaging (and dispensing) on the cost effectiveness of duodenal ulcer therapy.

From an MOH+ perspective, cost-effectiveness results indicate that RAN-BMT is the least costly of the 5 regimens but also has the lowest effectiveness (49 weeks per year without ulcer versus 51 weeks per year with the PPI-based regimens). There was very little difference in the expected number of weeks without ulcer between the PPI-based regimens. Amongst these regimens, PPI-CM is the least costly strategy and yields a cost-effectiveness ratio of $Can5.77 compared with RAN-BMT.

From an MOH– perspective, RAN-BMT remains the least costly regimen but the rank ordering of Hp-PAC® and PPI-CM change. Hp-PAC® yields a cost-effectiveness ratio of $Can5 per ulcer week averted compared with RAN-BMT.

The incremental cost effectiveness of Hp-PAC® and PPI-CM largely depends on the dispensing fees. The $Can2 difference in 1-year expected costs between PPI-CM and Hp-PAC® hinges on the inclusion of the $Can2 copayment.

Regardless of the perspective, there is only an annual $Can2 cost difference per patient between PPI-CM and Hp-PAC® which, coincidentally, is similar to the $Can2 dollar copayment in Ontario. Given the various uncertainties and assumptions made in the decision model, it is difficult to assess if this difference is robust. For example, from an MOH+ perspective, when omeprazole is used as the PPI in all PPI-based regimens (except Hp-PAC®), the expected costs for PPI-CM and the Hp-PAC® are identical. In addition, if the PPI-CM eradication is lowered from 90 to 88% (i.e. to equal the eradication of Hp-PAC®), Hp-PAC® becomes the least costly strategy. Finally, our model did not adjust for potentially enhanced compliance with the Hp-PAC®.

From our sensitivity analyses, the model is sensitive to changes in the PPI-AM eradication rate. However, PPI-AM is still dominated despite an increase in eradication from 71 to 77%.

Metronidazole and/or clarithromycin resistance rates are important factors that can alter the *H. pylori* eradication rate of a given strategy. To properly address resistance, both the proportion of patients with the resistant organism and the eradication rate given resistance are needed. As we have shown, there is a direct relationship between eradication rate and expected costs and effects. However, the true impact of antibacterial resistance on *H. pylori* eradication rates is less clear. In addition, we do not know the proportion of patients with resistant organisms that are included in the base case eradication rate assumptions.

There are a number of limitations to our analysis including: (i) use of confirmed duodenal ulcer patients (rather than a dyspeptic patient population); (ii) the assumption that the *H. pylori* eradication rate for Hp-PAC® was equal to that of PPI-CA

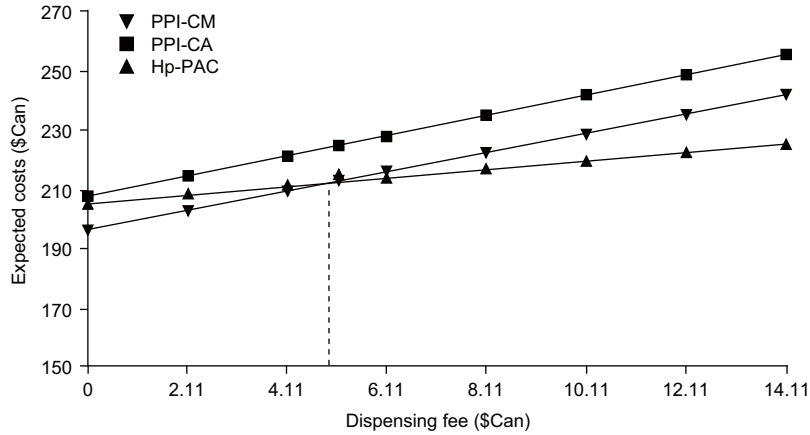

Fig. 3. Sensitivity analysis on the effect of dispensing fees on expected costs of PPI-CM, PPI-CA and Hp-PAC® (MOH+ perspective; patient copayment held constant at 0). The broken line indicates the threshold dispensing fee of $Can4.92 that would equalise the expected costs of Hp-PAC® and PPI-CM. **Hp-PAC®** = lansoprazole-clarithromycin-amoxicillin, prepackaged; **MOH+** = Ontario Ministry of Health perspective excluding the patient copayment; **PPI** = proton pump inhibitor; **PPI-CA** = PPI-clarithromycin-amoxicillin; **PPI-CM** = PPI-clarithromycin-metronidazole; **$Can** = Canadian dollars.

(which may not be justified if the Hp-PAC® is associated with greater compliance and hence greater efficacy); (iii) limited generalisability beyond Ontario, Canada; (iv) not addressing antibacterial resistance; and (v) not examining the impact of Hp-PAC® on patient compliance. Both of these last 2 factors are likely to be in favour of the Hp-PAC® and therefore our current analysis might be considered conservative with respect to Hp-PAC®. To address such limitations, further clinical and economic research in this area is necessary.

Conclusion

Using the example of *H. pylori* eradication for ulcers, we have shown that, in jurisdictions where pharmacists are reimbursed for each drug item within a dispensed prescription, the introduction of pre-packaged multidrug regimens has the potential to bring cost savings to both insurers (public or private) and patients. In the specific comparison of Hp-PAC® versus PPI-CM, incremental costs are sensitive to the level of dispensing fee and patient copayment.

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