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A Randomized Trial Comparing Omeprazole, Ranitidine, Cisapride, or Placebo in *Helicobacter pylori* Negative, Primary Care Patients with Dyspepsia: The CADET-HN Study

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BACKGROUND: The management of *Helicobactor pylori* negative patients with dyspepsia in primary care has not been studied in placebo-controlled studies.

METHODS: *H. pylori* negative patients with dyspepsia symptoms of at least moderate severity ($\geq$4 on a seven-point Likert scale) were recruited from 35 centers. Patients were randomized to a 4-wk treatment of omeprazole 20 mg od, ranitidine 150 mg bid, cisapride 20 mg bid, or placebo, followed by on-demand therapy for an additional 5 months. Treatment success was defined as no or minimal symptoms (score $\leq$ 2 out of 7), and was assessed after 4 wk and at 6 months.

RESULTS: Five hundred and twelve patients were randomized and included in the intention-to-treat (ITT) analysis. At 4 wk, success rates (95% CI) were: omeprazole 51% (69/135; 43–60%), ranitidine 36% (50/139, 28–44%), cisapride 31% (32/105, 22–39%), and placebo 23% (31/133, 16–31%). Omeprazole was significantly better than all other treatments ($p < 0.05$). The proportion of patients who were responders at 4 wk and at 6 months was significantly greater for those receiving omeprazole 31% (42/135, 23–39%) compared with cisapride 13% (14/105, 7–20%), and placebo 14% (18/133, 8–20%) ($p = 0.001$), but not ranitidine 21% (29/139, 14–27%) ($p = 0.053$). The mean number of on-demand study tablets consumed and rescue antacid used was comparable across groups. Economic analysis showed a trade-off between superior efficacy and increased cost between omeprazole and ranitidine.

CONCLUSION: Treatment with omeprazole provides superior symptom relief compared to ranitidine, cisapride, and placebo in the treatment of *H. pylori* negative primary care dyspepsia patients.

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INTRODUCTION

Dyspepsia, a common condition found in up to 40% of the general population, decreases a person's quality of life (1). In Canada, 7% of family practitioner (FP) visits are for dyspepsia (2). Dyspepsia is not a diagnosis, but rather describes a number of symptoms that are thought to originate in the upper gastrointestinal tract (3, 4). The primary symptom is epigastric pain or discomfort and other symptoms include excessive burping/belching, upper abdominal bloating, nausea, and feeling of abnormal or slow indigestion or early satiety. Canadian FPs consider heartburn and acid regurgitation as accompanying symptoms of dyspepsia (4). Dyspepsia-related health care costs are high due to diagnostic investigations, prescribed medications, and increased absenteeism from work (5).

Symptom-based diagnosis using dyspepsia subgroup approaches has been shown to be unreliable (3, 6, 7). This is largely because of the considerable overlap of symptoms among patients with peptic ulcer disease, gastro-esophageal reflux disease, functional (non-ulcer) dyspepsia, and other diagnoses, whereby any single symptom or subgroup of symptoms is not predictive of the diagnosis.

In the CADET-HP study, we have shown that in *Helicobacter pylori* positive patients with uninvestigated dyspepsia, cure of the infection leads to improvement in symptoms and is cost-effective (8, 9). In this study, we explore the

management of the same patients, but those who are *H. pylori* negative.

The objective of the study was to compare the efficacy of omeprazole, ranitidine, and cisapride to placebo in *H. pylori* negative dyspepsia patients at 4 wk and 6 months. Our hypothesis was that omeprazole would be superior to the other three treatments.

METHODS

Study Design

This was a multicenter, double-blind, placebo-controlled, parallel design study. Allocation to treatment was assigned in equal numbers (1:1:1:1) using a central computer-generated randomization list stratified for each center in blocks of four. All research personnel and patients remained blinded to the treatment allocation for the duration of the study. Patients were enrolled at 35 primary care centers across Canada from September 1998 until February 2001. The study protocol was approved by local Ethics Committees, and written informed consent was obtained from each patient.

Selection of Patients

With the exception of *H. pylori* status, the inclusion and exclusion criteria were similar to the CADET-HP Study (8). Patients had to have epigastric pain or discomfort with or without heartburn, acid regurgitation, excessive burping or belching, increased abdominal bloating, nausea, feeling of abnormal digestion, or early satiety. The family physician needed to be confident that patient was suitable for empiric treatment. Patients with alarm symptoms (such as vomiting, evidence of bleeding, inadvertent weightloss, dysphagia) warranting an endoscopy, a previous diagnosis of gastroesophageal reflux disease (GERD) by endoscopy or x-ray, and those with heartburn and/or regurgitation alone without epigastric pain were considered to have a diagnosis of GERD, and were excluded. Patients were also excluded if they had investigations by upper endoscopy and/or GI barium study within 6 months prior to randomization or on more than two separate occasions within the proceeding 10 yr. The presence of all Manning criteria was recorded at baseline. Patients who fulfilled the Manning criteria ($\geq$3/6) for irritable bowel syndrome were excluded (10).

A serological test (Helisal^{TM}—Rapid Blood Test or One Step Test, manufactured by Cortecs Diagnostics Ltd, UK) was used to assess *H. pylori* status. A negative serological test was confirmed by a negative validated ^{13}C-Urea Breath Test (LARA test, Alimenterics New Jersey (11) or HELIKIT test, Isotechnika, Edmonton, Canada) (12).

Study Protocol

Following a 2-wk period of observation during which baseline severity of symptoms was recorded, eligible patients were randomized to a 4-wk treatment course with omeprazole 20 mg (as one tablet) once a day, ranitidine 150 mg (as one tablet) twice a day (bid), cisapride 20 mg (as 2 $\times$ 10 mg tablets) bid or placebo. Identical looking dummy tablets were used. A triple dummy technique was used so that each patient received one active dose in both the morning and evening. For the omeprazole group, a dummy tablet was used for the evening dose. Randomization was concealed from patients, study personnel, and investigators. Following the initial 4-wk treatment period, and irrespective of symptom improvement, patients continued with the same medication during a 5-month, on-demand phase. In the on-demand phase, patients took medication for as long as was needed if their symptoms persisted or reoccurred to a daily maximum equivalent to that ingested in the initial 4 wk for omeprazole and ranitidine and or in the case of for cisapride, to a maximum of 10 mg bid. Data on time to relapse were not collected. Regular strength Mylanta tablets (Warner-Lambert Canada Inc.) were allowed as rescue medication up to four times a day during both the initial and on-demand treatment phases

Patient compliance with the protocol (first 4 wk) and drug use (on-demand phase) was assessed using pill count of returned medication. Patients were considered to have compliant during the initial 4 wk of treatment if they had taken at least 75% of the dispensed tablets.

Patients visited the clinic at randomization, and after 4, 12, and 24 wk, and were contacted by telephone at 8, 16, and 20 wk following randomization. Throughout the course of the on-demand study phase, patients were managed by their FP according to their usual practice. FPs were allowed to give other prescription drugs for dyspepsia as well as order investigations such as endoscopy or x-rays. Results of endoscopy or x-rays were not tracked as part of the study. Recurrent symptoms or ordering of GI-investigations did not result in discontinuation from the study. If medications other than study drugs were prescribed for dyspepsia, the study drugs were discontinued and the patient was classified as a treatment failure. These patients remained in the study and information regarding concomitant medications, tests performed, referrals to specialists, and adverse events was recorded.

Outcome Measures

GLOBAL OVERALL SYMPTOMS OF DYSPEPSIA. The primary outcome measure of the study was the Global Overall Severity (GOS) score. This measured dyspepsia symptoms over the preceding 4 wk using a seven-point Likert scale as employed in the CADET-HP trial (8). Severity ranged from 1) no problem, 2) minimal problem—can be easily ignored without effort, 3) mild problem—can be ignored with effort, 4) moderate problem—cannot be ignored but does not influence daily activities, 5) moderately severe problem—cannot be ignored and occasionally limits daily activities, 6) severe problem—cannot be ignored and often limits concentration on daily activities to 7) very severe problem—cannot be ignored and markedly limits daily activities and often requires rest. This seven-point scale was slightly amended from previously validated five- and seven-point scales (13, 14) and has been used in other dyspepsia studies (8, 15, 16). The main

reason for using a seven-point scale was that it is better able to detect smaller differences.

All enrolled patients had either epigastric pain or discomfort and a GOS score of at least moderate severity (4 of 7) over the month prior to randomization. For the *primary outcome measure*, treatment success was defined as a score of either 1 (none) or 2 (minimal) on the GOS scale after 4 wk of treatment and at the final 6 months visit. The proportion of patients becoming completely asymptomatic (GOS = 1) was also determined as a secondary outcome.

Other Symptoms

At each visit, including the baseline visit, patients were asked to rate the severity of a specific dyspeptic symptom (epigastric pain or discomfort, heartburn, regurgitation, upper abdominal bloating, excessive belching, nausea, and early satiety) over the previous month, using the same seven-point Likert scale used for the GOS. Patients also rated their three most bothersome symptoms. Based on the most severe symptom at baseline, patients were classified into ulcer-, reflux-, or dysmotility-like dyspepsia subgroups to explore the utility of such classification to predict treatment success. For ulcer-like dyspepsia, epigastric pain was most bothersome, for reflux-like dyspepsia, heartburn and/or regurgitation, and for dysmotility-like dyspepsia, upper abdominal bloating.

Quality of Life Measures

Quality of life was assessed using the same validated instruments as used in the CADET-HP study (8). These were the disease-specific, self-administered, "quality of life in reflux and dyspepsia" (QOLRAD) instrument (17), gastrointestinal symptoms rating scale (GSRS) (18), and overall treatment effect (OTE) (19).

Dyspepsia-Related Health Utilization Costs

Dyspepsia-related use of health resources was measured prospectively at monthly intervals by study personnel (telephone and clinic interviews) using the health resource utilization questionnaire, which was developed for the CADET studies. Direct and indirect costs were collected and aggregated in the same fashion as in the CADET-HP study (8, 9). All drug costs were included as part of the economic analysis. The drug costs excluding pharmacy dispensing fee were cisapride 20 mg twice a day $2.48, non-generic ranitidine (Zantac®) 150 mg twice a day $2.20, generic ranitidine 150 mg b.i.d. $0.80, and omeprazole 20 mg od $2.20. A 10% retail mark-up was added for all drug costs.

Study protocol visits were not costed. As all patients underwent UBT, their costs were not included. All costs are expressed in Canadian dollars. The Canadian dollar is worth approximately 0.75 U.S. dollar, 0.65 Euro, and 0.46 pound sterling. Due to the duration of the study, costs were not discounted.

The cost for each health resource was calculated from the volume of resources consumed and their unit prices to estimate total resource cost for each patient. For the primary economic analyses, indirect and direct costs (Province of Ontario, Canada, Ministry of Health (MOH) perspective) were aggregated to determine the societal perspective. The Ontario Ministry of Health covers most health care costs except for prescription drugs, which are only covered for patients equal to and over the age of 65 yr or if the patient was on social welfare. The MOH perspective then is analogous to situations with (for age $\geq$65) and without (for age $<$65) a private payer. The MOH perspective did not include the cost of OTC dyspepsia medications and indirect costs such as transportation and lost productivity.

The primary economic objective was to prospectively measure the costs of health resources consumed per patient over the 6 months of the study. For the economic evaluation of the study, we used the incremental cost effectiveness ratio (ICER) (20). The ICER is the difference in cost between treatments divided by the difference in effectiveness. The ICER measures the ratio of the additional cost of achieving one more treatment success as a result of eradication treatment. The cost-effectiveness is expressed as the cost per month free of symptoms. It assumes that those who were responders at 6 months were symptom-free throughout the trial. As the 95% confidence intervals around the ICER may be highly skewed, a bootstrap method was used to calculate 95% confidence intervals (21, 22). The same technique was used to create cost acceptability curves as described elsewhere (9).

Determination of Sample Size

Sample size calculation was based on estimates of the anticipated difference in treatment success rates between omeprazole and placebo. The assumed 4-wk treatment success for omeprazole was 31% and 16% for placebo (23). Assuming a 2-tailed alpha error rate of 0.05 and a power of 80% with a 15% dropout rate during screening, 135 patients were required for each treatment arm.

Statistical Evaluation

The ITT analysis included all randomized patients. A patient who discontinued at any time was considered a treatment failure. The proportion of patients with success was compared for all treatment groups using the Cochran-Mantel-Haenszel test. A global test using all treatment groups was initially performed. Subsequently, individual treatment groups were compared in a pair-wise manner. For numerical variables (QOLRAD, GSRS, and OTE), the change from baseline was analyzed using an ANCOVA model. For other numerical variables including average number of study tablets, simple T-tests were used. It was decided before the study started that the p-value for the main comparison using the GOS score be corrected for multiplicity using a Bonferroni correction and considered significant if $p < 0.01$. All other p-values for the primary outcome measure (GOS response at 4 wk and 6 months) were declared significant at $p < 0.05$. For the secondary analyses, no corrections were made for multiple testing.

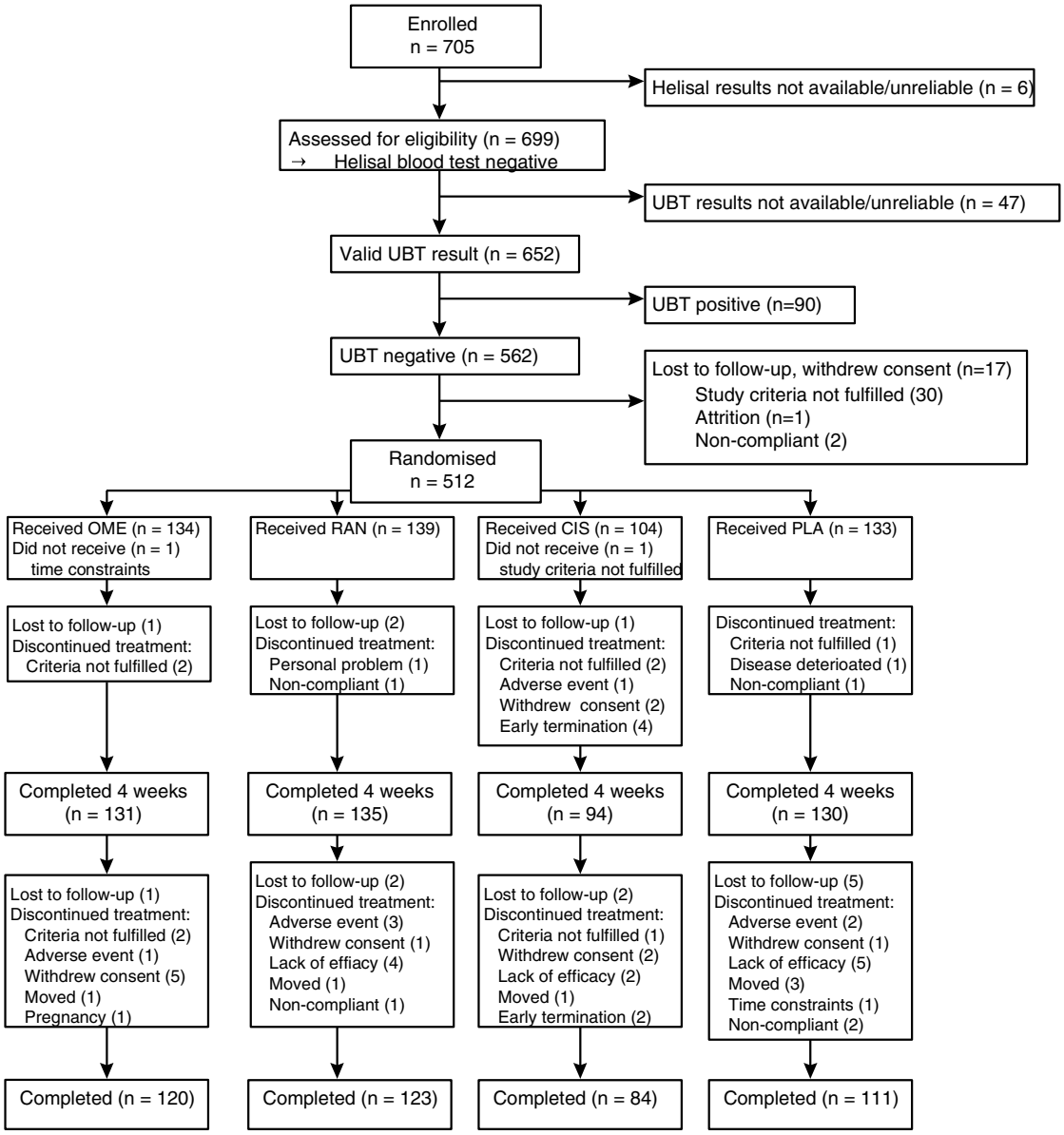

Figure 1. Flow diagram of study patients.

RESULTS

The flow chart in Figure 1 describes the patients through the study. Of the 705 patients who were enrolled at the baseline observation, 512 were randomized to one of the four treatment groups. In 90 patients (13.8%), serology was false negative as the UBT was positive and these patients were excluded. The false positivity rate of the Helisal test was not assessed as patients with positive serology were not further evaluated. After the initiation of the study, increased concerns were reported about rare, serious, cardiac side effects related to the use of cisapride (24). The steering committee decided to stop enrollment in the cisapride arm in January 2000. All patients who were taking cisapride were informed about these potential side effects and were withdrawn from the study. Therefore, fewer patients than planned were available in the cisapride treatment arm. Blinding of site personnel to study results for these patients was maintained until the end of the study.

Demographic baseline characteristics were well balanced in the ITT population (Table 1). At baseline there were no statistically significant differences among the treatment groups including symptoms. Epigastric pain/discomfort was most frequently ranked (40%) as the most bothersome symptom followed by heartburn (25%) and bloating (13%) (Fig. 2). The average duration of dyspepsia was 8 yr.

Results at Four Weeks

Compliance, as measured by pill count, was high during the 4-wk treatment phase as shown in Table 1.

Omeprazole was superior to the other drugs, and ranitidine was better than placebo (Fig. 3A and B) when considering

Table 1. Demographic Characteristics of the ITT Population at Baseline

	OME	RAN	CIS	PLA
N	135	139	105	133
Male				
n (%)	61 (45)	65 (47)	42 (40)	71 (53)
Race				
Caucasian	130	136	101	126
Other	5	3	4	7
Current smoker				
n (%)	47 (35)	44 (32)	32 (30)	31 (23)
Age (yr)				
Mean	42	43	40	41
Range	19–77	18–78	18–69	18–72
Duration of symptoms (yr)				
Mean number of patients	8.4	8.5	9.9	8.9
Duration 3–12 months	18	20	13	16
1–5 yr	44	49	31	51
>5 yr	73	70	61	66
Compliance with medications				
% Taken*	91	94	84	90

*Patients withdrawn due to early termination of the cisapride arm were not included in the compliance calculation.

both the primary outcome measure of GOS ≤ 2 as well as complete (GOS = 1) symptom relief. For responders (GOS $\leq$ 2) the results were omeprazole 51.1% (69/135, 95% CI 42.7–54.5%), ranitidine 36.0% (50/139, 28.0–43.9%), cisapride 30.5% (32/105, 21.7–39.3%), and placebo 23.3% (18/133, 16.1–30.5%). Based on the difference in success rates between omeprazole (51%) and placebo (23%), the number needed to treat (NNT) to achieve one treatment success was 4 (95% CI 3–6). When omeprazole was compared to ranitidine, the NNT was 7 (95% CI 4–29). For complete responders (GOS = 1), the results were omeprazole 23.7% (32/135, 95% CI 16.5–30.9%), ranitidine 10.8% (15/139, 5.6–15.9%), cisapride 7.6% (8/105, 2.5–12.7%), and placebo 3.8% (5/133, 0.5–7.0).

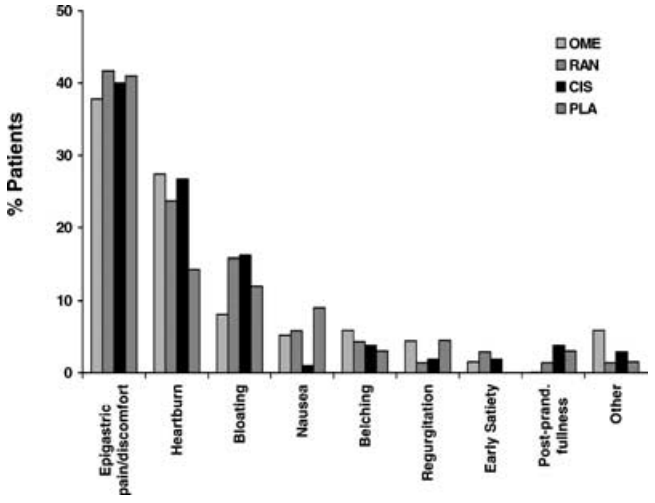

Figure 2. Frequency of most bothersome symptom at baseline; ITT.

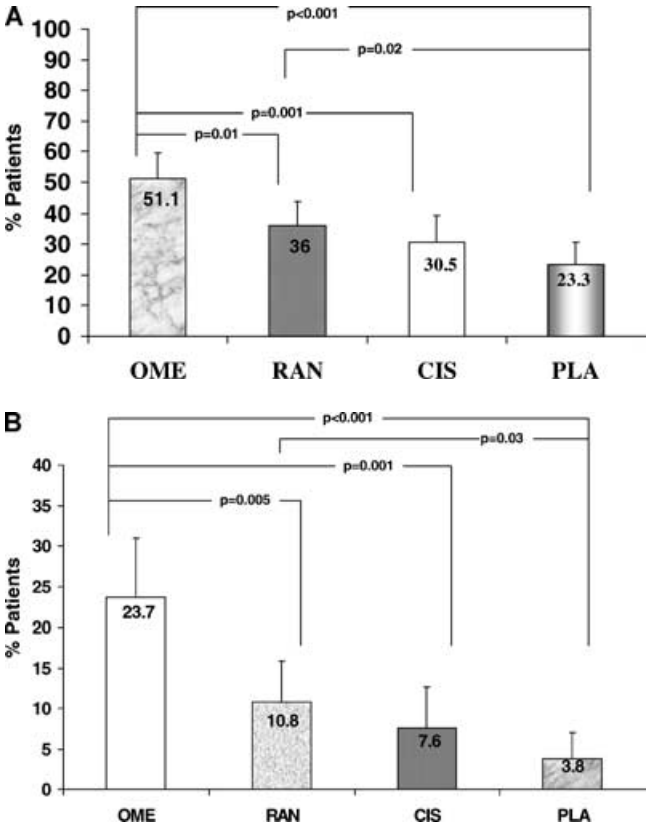

Figure 3. (*A*) Proportion of patients with treatment success (GOS $\leq$2) at 4 wk; ITT. (*B*) Proportion of patients with complete relief (GOS = 1) at 4 wk; ITT.

A number of subgroup analyses were performed, but the study was not powered for these. These analyses were not corrected for multiple comparisons. In those patients who had either no or minimal heartburn and/or regurgitation at baseline (n = 301), omeprazole and ranitidine were superior to placebo. The results were omeprazole 48.7% (38/78, 95% CI 37.6–59.8%), ranitidine 39.5% (32/81, CI 28.9–50.2%), cisapride 33.9% (21/62, CI 22.1–45.7%), and placebo 21.3% (17/80, CI 12.3–30.2%). For patients with at least mild heartburn and/or regurgitation (score $\geq$ 3) at baseline (n = 211), omeprazole was more effective than the other treatments (Fig. 4). The results were omeprazole 54.4% (31/57, 95% CI 41.5–57.3%), ranitidine 31% (18/58, CI 19.1–42.9%), cisapride 25.6% (11/43, CI 12.5–38.6%), and placebo 26.4% (14/53, CI 14.5–38.3%).

In approximately 25% of the patients, heartburn was the most bothersome symptom. If these patients are excluded, the results in the remaining 378 patients were omeprazole 42.7% (41/96), ranitidine 36.8% (39/106), cisapride 28.9% (22/76), and placebo 25% (25/100). The results of omeprazole versus placebo were statistically significant, $p = 0.009$. The difference between ranitidine and placebo was just above the conventional level of significance ($p = 0.068$) as was the difference between omeprazole and cisapride ($p =$

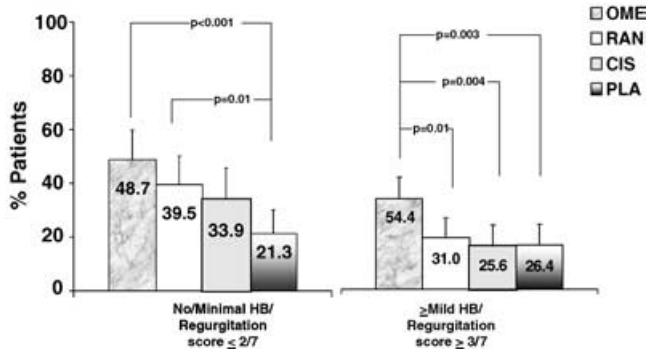

Figure 4. Proportion of patients with treatment success according to heartburn severity; ITT.

0.064). Other comparisons were not statistically significantly different.

In patients who rated epigastric pain as their most bothersome symptom, omeprazole (47%, 23/49) was also superior compared to the other treatments: cisapride (23%, 10/43, $p = 0.02$), and placebo (25%, 14/55, $p = 0.02$), but not compared to ranitidine (39%, 23/59, $p = 0.4$). In patients who rated heartburn and/or regurgitation as their most bothersome symptom, omeprazole (68%, (30/44)) was superior compared to the other treatments: ranitidine (37% (13/35), $p = 0.006$), cisapride (33% (10/30), $p = 0.003$), and placebo (15% (6/39), $p < 0.001$). There were too few patients who rated upper abdominal bloating as their most bothersome symptom to permit useful statistical analysis.

Results at Six Months

The proportions of responders at 6 months were (proportion; 95% CI) omeprazole 44% (60/135; 36–53%), ranitidine 41% (57/139; 33–49%), cisapride 40% (42/105; 31–49%), and placebo 35% (46/133; 27–43%). None of the differences were statistically significant. The proportions of patients who were *responders at 4 wk* and remained *responders at 6 months* were (proportion; 95% CI) omeprazole 31.1% (42/135; 23–39%), ranitidine 20.9% (29/139; 14–27%), cisapride 13.3% (14/105; 7–20%), and placebo 13.5% (18/133; 8–20%) (Fig. 5). The differences between omeprazole and both cisapride and placebo were statistically significant ($p = 0.001$), while the difference between omeprazole and ranitidine was not statistically significant ($p = 0.053$). The proportions of patients who were responders at 6 months but nonresponders at 4 wk were omeprazole 13%, ranitidine 20%, cisapride 27%, and placebo 22%.

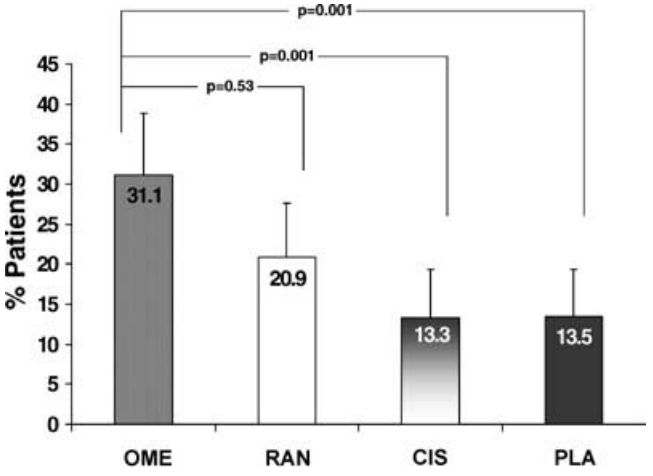

Figure 5. Proportion of patients who were responders at 4 wk and 6 months (ITT).

Only 2–4% of patients took no further study drug in the on-demand phase. Figure 6A shows that 4-wk responders in all active treatment arms took an average of one treatment dose every second day, which was slightly fewer than nonresponders. Placebo-treated patients took approximately one tablet each day. Rescue antacid use was significantly less for 4-wk responders than nonresponders in the omeprazole, cisapride, and placebo groups (Fig. 6B). There was no difference in the median time to relapse (first "on-demand" dose) among groups.

Other Outcome Measures

During the study 65 (13%) patients developed IBS as assessed by ≥3 Manning criteria recorded at any of the follow-up visits. The percentages of patients with 0, 1, or 2 Manning

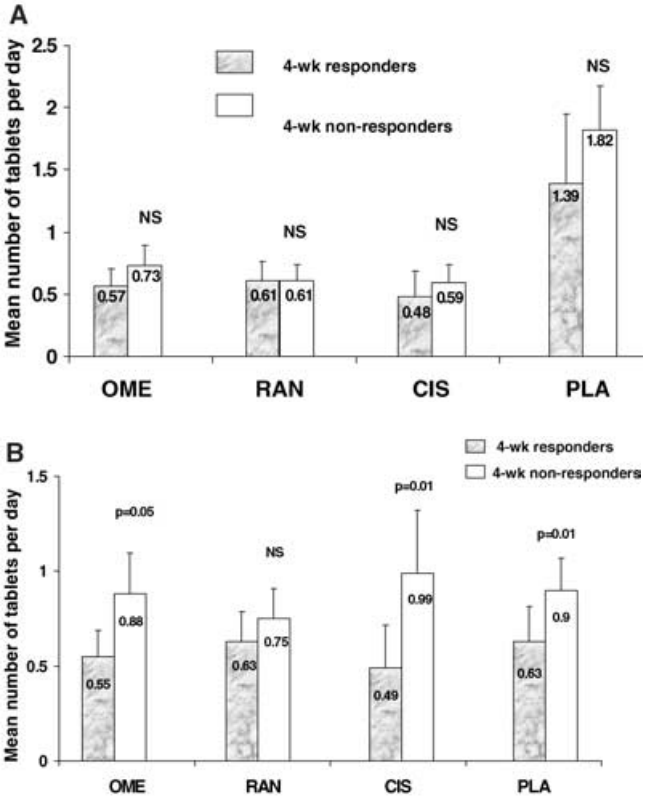

Figure 6. (*A*) Mean number of study tablets/day during the on-demand period; ITT. (*B*) Mean number of Mylanta tablets/day during the on-demand period; ITT numbers.

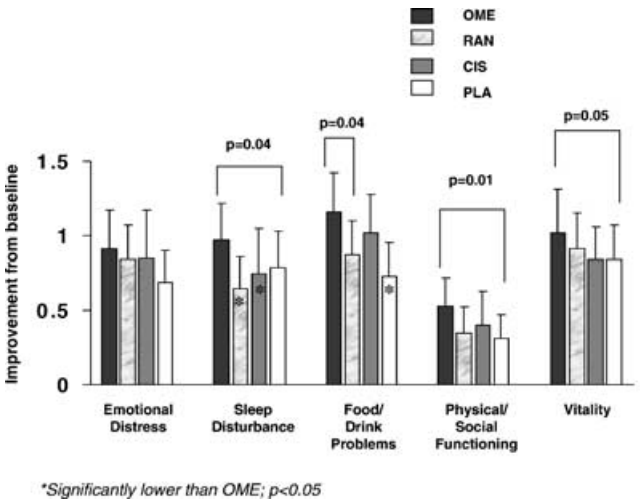

Figure 7. QOLRAD results at 4 wk; ITT.

criteria at baseline were 52, 30, and 18%, respectively. The presence of Manning criteria at baseline was not a predictor of treatment response after 4 wk and at 6 months in logistic regression analysis. The response rate at 4 wk and 6 months for patients who developed ≥3 Manning criteria (overall 19% and 11%, respectively) during follow-up was lower compared to patients with <3 Manning criteria at 4 wk and 6 months.

Quality of Life Outcome Measures

At the end of the 4-wk treatment period, omeprazole significantly improved quality of life compared to placebo for all QOLRAD dimensions, except for emotional distress (Fig. 7). There were other slight improvements with omeprazole compared to both ranitidine and to cisapride. Among the 4-wk responders, the omeprazole arm benefit in the sleep disturbance domain at 4 wk was lost at 6 months, while improvements over placebo in the other domains were maintained (data not shown).

At 4 wk, omeprazole significantly improved quality of life compared to all other treatments for GSRS overall, and the indigestion and reflux domains of the GSRS. Cisapride and placebo also improved the reflux dimension (data not shown). Among the 4-wk responders, initial improvements in GSRS scores were not maintained at 6 months except for omeprazole compared to placebo in the reflux dimension. It is worth mentioning that the GSRS is not a true quality of life instrument as it only measures severity of GI-related symptom and not their impact on quality of life.

After the 4-wk treatment period, a statistically significant difference in OTE was seen in favor of omeprazole compared with the other treatments. During the on-demand phase there was a decrease in the number of patients who rated themselves as better which correlated with an overall decrease in patient responders at 6 months when compared to 4 wk (data not shown). The results after 2 and 5 months of on-demand therapy were similar.

Table A1. Total Mean Societal Cost per Patient in Canadian Dollars During the 6 Months Following Randomization; ITT Population

	OME (n = 135)	RAN (n = 139)	CIS (n = 105)	PLA (n = 133)
Mean	364	225	371	152
SD	285	439	1109	363
Median	286	130	186	33
Min	0	4	0	0
Max	2389	4,734	11,218	2,621

Table A2. Total Ministry of Health Cost in Canadian Dollars During the 6 Months Following Randomization; ITT Population

	OME (n = 135)	RAN (n = 139)	CIS (n = 105)	PLA (n = 133)
Mean	28	28	68	28
SD	98	93	529	127
Median	0	0	0	0
Min	0	0	0	0
Max	767	710	5,422	1,296

Table A3. Selected Values of Direct and Indirect Costs

Item	Costs (Canadian $)*
Hospitalization cost‡	432.05 per day
Doctor visits	
Family practitioner	All visits 16.25
Gastroenterologist	First visit 106.95, subsequent 23.45
Surgeon	First visit 55.90, subsequent 19.20
Nurse visit§	37.27 per visit
Endoscopy¶—physician charge	94.60
UGI barium meal¶—physician charge	84.85
13C-UBT‖	80.00
Laboratory tests** (selected tests)	Cost is $/test
CBC	8.77
Creatinine	2.74
Blood sugar	1.88
Helisal rapid whole blood test	22.00
Lost productivity†	
Male 0–19, female 0–19	31.67/day, 20.13/day
Male 20–65, female 20–65	79.39/day, 73.84/day
Male >65, female >65	19.27/day, 21.61/day

**1 Canadian $ ≅ 0.60 U.S.$ ≅ 0.43 U.K.£.

†Ontario Drug Benefit Formulary/Comparative Drug Index. Ontario Ministry of Health 35, Toronto, Canada, 1999. Prices include a 10% retail markup. Non-prescription drug costs were determined from the Medis Health and Pharmaceutical Services Inc. Distributing Catalogue, Montreal, Canada, 1999.

‡Canadian Coordinating Office for Health Technology Assessment (CCOHTA). A Manual of Standard Costs for Pharmacoeconomic Studies in Canada: Feasibility Study. Ottawa, Canada, 1995. www.ccohta.ca.

¶OHIP Schedule of Benefits: Physician Services under the Health Insurance Act, 1999. Toronto, Canada.

§Ontario Ministry of Health. System-Linked Research Unit. Approach to the measurement of costs (expenditures) when evaluating Health and Social Programmes, 1995, McMaster University, Hamilton, Ontario, Canada.

‖MDS Laboratories charge, Ontario, Canada.

**Ontario Ministry of Health. OHIP Schedule of Laboratory Services, 1999, Ontario, Canada.

††Labor force and unpaid work of Canadians: selected labor force, demographic, cultural, educational, and income characteristics by sex (based on the 1991 standard occupational classification) for Canadian provinces, territories, and CMAs, 1996 census (20% sample data). Statistics Canada CD-ROM, Ottawa, 1996.

Table 2. Resource Utilization (Frequency up to 6 Months)

	OME	RAN	CIS	PLA
GP visits	29	37	38	44
Specialist visits	8	17	5	6
Endoscopy/x-ray/lab tests/other procedures	8	27	10	13
Prescriptions for dyspepsia	20	28	26	35
Productivity loss (# work days missed)	61	102	129	106

Adverse Events

Adverse events, although frequent, were generally mild. Only two patients stopped the study drug due to serious adverse events. One patient on ranitidine was diagnosed with prostate cancer. One patient receiving placebo suffered a myocardial infarction from which he recovered. This occurred at 8 wk into the study when the patient presented with sudden onset of chest pain. This pain was different from the dyspepsia symptoms the patient had been complaining of at study entry. The investigator considered a relation with study drug was unlikely.

Health Economic Results

Total mean societal cost and MOH perspective per patient are listed in Tables A1 and A2 based on costing data presented in Table A3. Few patients were referred to specialists or had investigations and other outcomes such as need for additional prescriptions for dyspepsia and productivity loss all were relatively low (Table 2). Therefore, the main driver of cost in these patients was the costs of the medications.

Table 3 shows ICERs and 95% confidence intervals for the health resource costs at 6 months for the three active treatments relative to placebo. Cisapride had the least favorable ICER. Furthermore, the 95% confidence interval was very wide, which was in part explained by low efficacy. Based on the ICER, generic ranitidine was the cheapest treatment option although the 95% confidence interval with omeprazole overlapped.

Figure 8 shows the placebo adjusted cost-effectiveness acceptability curves of omeprazole and ranitidine, which were created using the bootstrap technique. Data on cisapride are not shown as in all analyses, cisapride relative to ranitidine and omeprazole was not cost-effective because of high cost of the drug and low efficacy. As can be seen in Figure 8, the probability of omeprazole being cost-effective relative to ranitidine is 30% if willingness to pay (WTP) is zero dollars. Figure 8 also shows that the probability of being cost-effective is higher for ranitidine below a WTP of approximately \$154 per month. (At \$154, the probability of either omeprazole or ranitidine being cost-effective is 50%.) Above \$154, the probability of being cost-effective is higher for omeprazole. One of the possible reasons for this high cost is that the success rate of both omeprazole and ranitidine decreased significantly when patients were switched from continuous therapy to on-demand. The possibility that the probability of cost-effectiveness of omeprazole relative to ranitidine is adversely affected by the decrease in response rates during the on-demand phase was explored by limiting the analysis to only those patients who were responders at 4 wk. This analysis did not substantially alter the results including the WTP (data not shown).

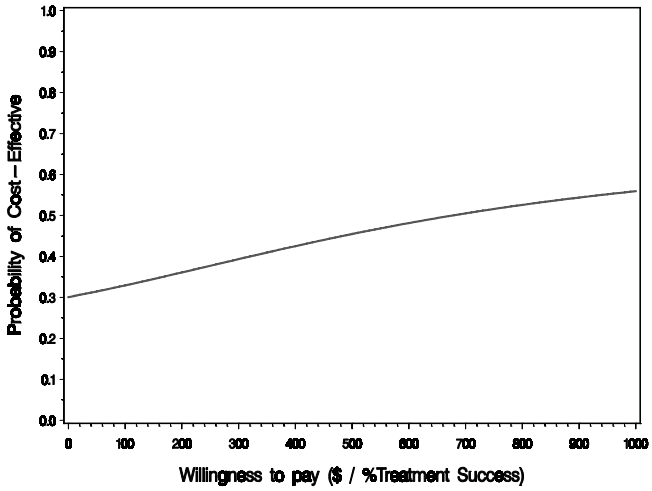

Figure 8. Bootstrapped cost-effectiveness acceptability curves of omeprazole and ranitidine. Cost and efficacy taken at 6 months. WTP is calculated per month. The y-axis shows the probability of omeprazole being cost-effective relative to ranitidine for different amounts a person is willing to pay per month. For example, if one is not willing to pay anything the probability of omeprazole being cost-effective relative to ranitidine is 30%. If one is willing to pay \$154 per month, the probability of omeprazole being cost-effective is equal (50%) to ranitidine. If WTP increases above this, the probability of omeprazole being cost-effective is approximately 60%.

DISCUSSION

Most clinical trials investigating management strategies for dyspepsia have been carried out in gastroenterology clinics,

Table 3. Incremental Cost Effectiveness Ratios (ICER) for 4-wk Treatment Responders Over the 6-Month Period for a Willingness to Pay of \$154, the Probability of Being Cost-Effective is Equal for Omeprazole and Ranitidine. The Total Cost of Omeprazole Minus Total Cost Ranitidine is \$ 139 (364 − 225). The Difference in Efficacy Between Omeprazole and Ranitidine Is 0.15 (0.51 − 0.36). Thus, the Incremental Cost Effectiveness Between Ranitidine and Omeprazole Is \$154 (139 Divided by 0.15 × 6)

Treatment (Ordered by Increasing Efficacy)	Total Cost	ΔCost	Effect	ΔEffect (GOS ≤ 2)	ICER (95% CI)
CIS	371	223	0.31	0.075	2988 (−4,365; 143,487)
Generic H2-RA	225	73	0.36	0.13	574 (−140; 4,057)
OME	364	212	0.51	0.28	762 (421; 1,426)
PLAC	152		0.23		

and not at the primary care level (3, 4, 25). The few available studies have been done in investigated (functional) dyspepsia patients. In functional dyspepsia patients, proton-pump inhibitors (26, 27), H_2-blockers (27–29), and cisapride (29, 30) appear to be effective in varying degrees.

This trial is the first randomized study carried out in primary care in which omeprazole, ranitidine, cisapride, and placebo are compared head-to-head in *H. pylori* negative primary care dyspepsia patients. Cisapride was given as a bid dose as this was commonly used in practice and compliance would have been less of an issue than qid dosing. After 4 wk of continuous treatment, omeprazole was clinically superior to ranitidine, cisapride, and placebo with respect to the primary outcome measure, the GOS—a validated seven-point Likert scale rating the patient's severity of dyspepsia (13, 14). Other dyspepsia studies have used a similar seven-point scale (8, 15, 16). The results were consistent for a number of different outcome measures including quality of life as assessed by the QOLRAD (17) and GSRS (18), both well validated quality of life and symptom-based outcome measures of upper GI-disorders, and for OTE. Omeprazole was also superior at 6 months among 4-wk responders. When all patients at 6 months were considered, results among the four treatment groups were similar. We believe the 6-month results for patients who were also responders at 4 wk are more clinically relevant as it would be unlikely that the physician and patient would start on demand treatment if symptoms were not resolved after 4 wk of continuous treatment. Other studies in primary care support the suggestion that proton-pump inhibitors (PPIs) are superior in treating patients with uninvestigated upper gastrointestinal symptoms, although they did not include a placebo group (31–33).

Our results support the use of a proton-pump inhibitor as the initial treatment for dyspepsia patients in primary care. Omeprazole with 51% was clearly the superior treatment, but as the definition of a responder was so stringent, 49% remained nonresponders. In practice, the number of patients with improvement would be higher as patients who improved from, for example, a score of 5 to 3 would report feeling better but in the context of this study would have been counted as a treatment failure.

As has been reported by others (3, 6, 7), patients had a multiplicity of symptoms leading to considerable overlap among dyspepsia subgroups. We found that omeprazole was superior for those patients who rated epigastric pain/discomfort and heartburn/regurgitation as their most bothersome symptom. In the dysmotility subgroup, the number of patients was too small to make a meaningful comparison between treatments. However, as the study was not powered for these subgroups and these secondary analyses were not corrected for multiple comparisons, the results should be interpreted with caution.

In patients presenting with a symptom complex of upper GI-symptoms, there has been much discussion about the definition of dyspepsia (3, 4). Many investigators and regulatory agencies have adopted the ROME criteria. An important aspect of both the old (34) and updated (35) ROME criteria for dyspepsia is that the symptoms heartburn and acid regurgitation are excluded from the dyspepsia definition, as they are considered to be part of GERD. We used the CanDys dyspepsia definition which includes the symptoms heartburn and regurgitation (4). That this dyspepsia definition is more practical in primary care is supported by the results of a related study of prompt endoscopy (the CADET-PE study) in patients with uninvestigated dyspepsia (7). In this study, there was extensive overlap among subgroups, which did not help in predicting endoscopic abnormalities, including esophagitis. Other studies have found similar results (36, 37). Using the CanDys definition of dyspepsia, we showed that in the related CADET-Hp study (8), *H. pylori* eradication resulted in improvement of dyspepsia up to 1 yr following eradication even in patients who had epigastric pain and dominant symptoms of heartburn. Other studies support that heartburn should not be separated from dyspepsia (36–40). Importantly, patients in our study needed to have moderate severity of epigastric pain. Patients with isolated heartburn or regurgitation without associated epigastric pain or a previous GERD diagnosis could not be enrolled in the study. As we have found in other studies (7, 8), most patients had suffered from dyspepsia for years (average 8.4–9.9 yr).

It is well established that in patients with endoscopically proven reflux esophagitis or peptic ulcer disease both H_2-blockers and proton-pump inhibitors (PPI) are efficacious and that PPIs are superior to H_2-blockers. The important aspect of our study design is that patients apart from testing for *H. pylori* were uninvestigated and therefore it is unknown what proportion of patients had GERD or ulcers. In approximately 25% of patients, heartburn was the most bothersome symptom. If those patients were excluded, omeprazole was also the most effective treatment although the difference with ranitidine was not statistically significantly different.

After 4 wk of continuous treatment, omeprazole was superior to all other treatments in patients with at least mild heartburn (Fig. 4). In patients with no or minimal heartburn, omeprazole was also the most efficacious medication, albeit at slightly decreased levels of efficacy compared to historical results in previous studies in patients with moderate or more severe heartburn.

Our study did not have an age limit for enrollment. Various guidelines suggest that patients over age 50 yr should also be investigated (3), although this is based on expert opinion and despite good evidence that gastric or esophageal malignancy is unlikely if there are no alarm symptoms (3, 4, 41, 42). Our study was not designed to answer the question whether the age limit recommendation for endoscopy can be increased. The treating family physician needed to be comfortable to treat patients empirically and patients with alarm symptoms were not enrolled. Whether or not a patient is referred for endoscopy, in practice, most of these patients will receive treatment after the visit to the primary care physician and our study demonstrates that acid suppressive therapy is efficacious and that PPIs are superior.

Cisapride is no longer available in most markets. Prokinetic therapy, especially cisapride, was commonly prescribed in primary care for dyspepsia. Our study shows that using cisapride, results are inferior when compared to omeprazole.

An important observation in our study was that during the 5-month on-demand phase, only 2–4% of patients required no medication. This suggests that dyspepsia is a chronic condition in these patients. The overall success rate during the 5-month on-demand treatment phase was lower than that seen in the 4-wk continuous treatment phase, despite the fact that patients on average took only one active treatment dose every second day. Omeprazole was superior to cisapride and placebo, and a trend was also noted when compared to ranitidine. Similarly, 4-wk responders took only one tablet of rescue antacids every other day, which was lower than for nonresponders. Patients were instructed to take treatment when symptoms recurred and to take them as long as symptoms were present. The decrease in proportion of responders at 6 months suggests that patients tended to under-treat themselves. This is supported by data from the OTE analysis in which the proportion of patients responding "better" declined over time. There are two explanations for the data. One is that patients are willing to tolerate minor symptoms of dyspepsia. Secondly, it is possible that the rescue antacids decreased the need for medication by providing rapid symptom relief. Overall antacid use was low in all groups. Further studies are required to explore the discrepancy between incomplete symptom control and patient preference for on-demand therapy.

During the 6-month follow-up period additional visits for dyspepsia, need for referrals or investigations, or additional dyspepsia-related prescriptions were relatively low indicating that most health care costs in this patient group was for the cost of medication. It is possible that in part the low use of health resources was related to the study design as patients were regularly contacted by phone or seen at study-driven clinic visits. The ICER data and the cost-effectiveness acceptability curve demonstrate that there is a trade-off between increased efficacy and higher cost for omeprazole when compared to ranitidine. Cisapride clearly was not cost-effective compared to acid suppressive therapy given its low efficacy for a high cost. WTP was calculated per month of therapy, *i.e.*, WTP over the 6-month study duration was divided by six. With regard to omeprazole and ranitidine, below a WTP of approximately $154 the probability of cost-effectiveness is higher for ranitidine, above $154 the probability of cost-effectiveness is higher for omeprazole. The analysis assumes that those patients who were responders at 6 months were responders throughout the trial. One possible explanation is that the cost-benefit of omeprazole is underestimated as its efficacy dropped from 51% to 31% during the on-demand phase and nonresponders at 4 wk continued in the study taking study drug. In practice, only patients who derive benefit from continuous therapy will receive prescriptions for the same drug. However, if the analysis is limited to only patients who were responders at 4 wk the probabilities of cost-effectiveness and WTP did not change substantially (data not shown). Therefore, the drop in efficacy for both omeprazole and ranitidine at 6 months did not substantially affect the cost-effectiveness analysis. Caution is warranted in the interpretation of these data as the number of patients in this analysis is low. The data do suggest that the cost of on-demand omeprazole is quite high and may not be cost-effective compared to on-demand ranitidine. Studies should be designed to specifically answer this question. Also, the analysis is very sensitive to the costs of medication which may vary from country to country. Given our efficacy data and economic analysis, the decision about whether to start with an H_2-blocker or a PPI should take place after careful discussions between the physician and the patient about the advantages and disadvantages of available therapies taken into consideration the local prices of drugs.

In summary, the proton-pump inhibitor omeprazole was the best first line treatment when compared with ranitidine, cisapride, and placebo for primary care *H. pylori* negative dyspepsia patients. Omeprazole was also the most successful in patients who rated epigastric pain or heartburn as their most bothersome symptom. The cost-effectiveness analyses suggest that omeprazole becomes cost-effective over ranitidine at a relatively high cost of $154 per symptom-free month. This may indicate that on-demand omeprazole is not cost-effective compared to on-demand ranitidine in *H. pylori* negative uninvestigated dyspepsia. However, studies are needed which are designed to specifically look at cost-effectiveness.

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APPENDIX: ECONOMIC ANALYSIS

Direct costs included unscheduled dyspepsia-related visits to the physician (*i.e.*, gastroenterologist, surgeon, Family Physician) and other health care professionals (*e.g.*, nurse), any dyspepsia-related hospitalizations, medications (prescription, over the counter, OTC), and investigations (*e.g.*, lab tests, x-rays, endoscopy). The prices of prescription medications were obtained from the Ontario Drug Benefit Formulary and the Medis Distributing Catalogue and costed as the purchase price plus a dispensing fee. OTC medication costs were calculated based on the reported amounts paid by patients. Hospitalization costs were obtained from the Canadian Coordinating Office for Health Technology Assessment (CCOHTA); physician services costs were obtained from the Ontario Health Insurance Plan (OHIP) Schedule of Benefits; laboratory costs derived from the OHIP Schedule of

Laboratory Services; and costs of other health professional visits were obtained from McMaster University.

Indirect costs of transportation and lost productivity as a consequence of days lost due to dyspepsia are relevant costs to society. Employed patients reported the number of days missed from work; unemployed and senior patients reported days lost from usual activities due to dyspepsia. These were costed according to the human capital approach and each day absent was costed in CAD$, as follows: 0–19 yr old (male $31.67, female $20.13), 20–64 yr old (male $79.39, female $73.84), and for 65+ yr old (male $19.27, female $21.61).

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