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LACK OF EFFECT OF TREATING *HELICOBACTER PYLORI* INFECTION IN PATIENTS WITH NONULCER DYSPEPSIA

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ABSTRACT

Background It is uncertain whether treatment of *Helicobacter pylori* infection relieves symptoms in patients with nonulcer, or functional, dyspepsia.

Methods We conducted a double-blind, multicenter trial of patients with *H. pylori* infection and dyspeptic symptoms (moderate-to-very-severe pain and discomfort centered in the upper abdomen). Patients were excluded if they had a history of peptic ulcer disease or gastroesophageal reflux disease and had abnormal findings on upper endoscopy. Patients were randomly assigned to seven days of treatment with 20 mg of omeprazole twice daily, 1000 mg of amoxicillin twice daily, and 500 mg of clarithromycin twice daily or with omeprazole alone and then followed up for one year. Treatment success was defined as the absence of dyspeptic symptoms or the presence of minimal symptoms on any of the 7 days preceding the 12-month visit.

Results Twenty of the 348 patients were excluded after randomization because they were not infected with *H. pylori,* were not treated, or had no data available. For the remaining 328 patients (164 in each group), treatment was successful for 27.4 percent of those assigned to receive omeprazole and antibiotics and 20.7 percent of those assigned to receive omeprazole alone ($P=0.17$; absolute difference between groups, 6.7 percent; 95 percent confidence interval, −2.6 to 16.0). After 12 months, gastritis had healed in 75.0 percent of the patients in the group given omeprazole and antibiotics and in 3.0 percent of the patients in the omeprazole group ($P<0.001$); the respective rates of *H. pylori* eradication were 79 percent and 2 percent. In the group given omeprazole and antibiotics, the rate of treatment success among patients with persistent *H. pylori* infection was similar to that among patients in whom the infection was eradicated (26 percent vs. 31 percent). There were no significant differences between the groups in the quality of life after treatment.

Conclusions In patients with nonulcer dyspepsia, the eradication of *H. pylori* infection is not likely to relieve symptoms. (N Engl J Med 1998;339:1875-81.)

APPROXIMATELY one third of people in industrialized nations have recurrent dyspeptic symptoms, or dyspepsia, many of whom have no evidence of chronic peptic ulceration, reflux esophagitis, a malignant condition, or other defined organic disease.[1-4] The ambiguity in the diagnosis has led to the development of various definitions of dyspepsia, dyspeptic symptoms, and nonulcer, or functional, dyspepsia, based on available clinical, epidemiologic, and pathophysiologic data.[5] Nonulcer dyspepsia is defined as "persistent or recurrent abdominal pain or discomfort centered in the upper abdomen in patients who have no definite structural or biochemical explanation for their symptoms (e.g., peptic ulcer disease, gastroesophageal reflux disease, malignancy or pancreaticobiliary disease)."[6] The pathogenesis of nonulcer dyspepsia is unknown, but disturbances of visceral perception, gastric acid secretion, and gastroduodenal motility, as well as *H. pylori* infection, have been implicated.[7] The reported prevalence of *H. pylori* infection in patients with gastritis and nonulcer dyspepsia ranges from 30 to 70 percent.[3,8] As yet, however, it is uncertain whether *H. pylori* infection causes the dyspeptic symptoms in these patients.

We compared the effect of one week of treatment with omeprazole, amoxicillin, and clarithromycin with that of one week of treatment with omeprazole alone on the relief of symptoms, eradication of *H. pylori* infection, healing of gastritis, and quality of life in patients with nonulcer dyspepsia. Given the evidence that regression of *H. pylori*–induced gastritis could take at least 1 year after the successful cure of the infection,[9] we followed the patients for 12 months.

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*Other members of the Omeprazole plus Clarithromycin and Amoxicillin Effect One Year after Treatment Study Group are listed in the Appendix.

METHODS

Study Design

This randomized, double-blind study was conducted in numerous centers in Austria, Canada, Germany, Iceland, Ireland, South Africa, and Sweden between December 1995 and December 1997, according to the principles of good clinical practice and in accordance with the revised Declaration of Helsinki. The study protocol and patient information and consent form were approved by an independent ethics committee at each study center, and written informed consent was obtained from the patients before enrollment.

Selection of Patients

Patients who sought medical care for dyspeptic symptoms (specifically, pain or discomfort centered in the upper abdomen) that had been present for at least six months and who had no history of peptic ulcer disease or gastroesophageal disease were eligible for the study, provided they had normal endoscopic findings (i.e., five or fewer gastric erosions and no esophageal, gastric, or duodenal ulcers, esophageal or duodenal erosions, or Barrett's esophagus) and were *H. pylori*–positive on analysis with the rapid urease test (HUT, Astra, Wedel, Germany). After enrollment, blood samples were obtained for routine laboratory screening, to check for any chemical or hematologic abnormalities. Patients were given diary cards and asked to evaluate their dyspeptic symptoms at bedtime each evening for a run-in period of seven days, during which they received no treatment. The symptoms were graded with use of a validated seven-point Likert[10] scale as absent (score of 0), minimal (1), mild (2), moderate (3), moderately severe (4), severe (5), or very severe (6). Only patients with moderate-to-very-severe pain or discomfort centered in the upper abdomen on at least three days during the run-in period underwent randomization in blocks of two, according to a computer-generated list. Patients with unintentional weight loss, dysphagia, hematemesis, or any other signs indicating serious disease were excluded. Treatment with histamine H_2-receptor antagonists, prostaglandins, or prokinetic agents during the seven days before entry into the study was not permitted, nor was treatment with proton-pump inhibitors, antibiotics, or bismuth-containing compounds during the month before the study began.

Study Protocol

At the end of the one-week run-in period, patients who fulfilled the selection criteria were randomly assigned to one week of treatment with either 20 mg of omeprazole (Losec, Astra, Södertälje, Sweden) twice daily (morning and evening), 1000 mg of amoxicillin (Amimox, Astra) twice daily, and 500 mg of clarithromycin (Bremón, Abbott Laboratories, Madrid, Spain) twice daily or 20 mg of omeprazole twice daily, as well as placebo antibiotics. The treatments were given orally in a double-blind fashion, and active and placebo tablets were identical in appearance. The patients returned to the clinic after 1 week and 1, 3, 6, 9, and 12 months after the end of treatment.

Endoscopy, Biopsy, and the Urea Breath Test

Endoscopy and biopsy were performed before the run-in period and 3 and 12 months after treatment was completed. Two biopsy specimens of the antrum, corpus, and angulus were obtained for histologic analysis at each visit, and one additional specimen of the antrum and the corpus was obtained during the preliminary endoscopy for the rapid urease test. The patients also underwent a urea breath test[11] at the end of the run-in period and again 3 and 12 months after treatment to confirm their *H. pylori* status. Patients were regarded as positive for *H. pylori* at randomization if they had a positive rapid urease test and a positive urea breath test or abnormal histologic findings (or both). At the 3-month and 12-month follow-up visits, patients were regarded as positive for *H. pylori* if they had a positive urea breath test, abnormal histologic findings, or both. In the case of patients who did not take these tests or whose data were lost, the *H. pylori* status was defined as unknown. Neither the patients nor the investigators were aware of the patients' *H. pylori* status during the study.

Histologic Analysis

The biopsy specimens were embedded in paraffin and cut into 4-μm sections perpendicularly to the mucosal surface. They were then stained with hematoxylin and eosin and Warthin–Starry silver, and the severity of gastritis was graded according to the Houston modification of the Sydney system.[12]

Assessment of the Quality of Life

We assessed the patients' quality of life on four occasions during the study — at randomization, after the completion of treatment, and at the 6-month and 12-month follow-up visits — with the use of two validated questionnaires. The Gastrointestinal Symptom Rating Scale assesses the severity of indigestion, diarrhea, constipation, abdominal pain, and reflux, and scores can range from 1 (no symptoms) to 7 (severe symptoms).[13] The Psychological General Well-Being Index[14] measures subjective well-being in terms of anxiety, depressed mood, positive well-being, self-control, and general health and vitality. The worst possible score is 22, and the best possible is 132. We also assessed the overall effect of treatment 6 and 12 months after it had ended by comparing the severity of dyspeptic symptoms before and after treatment with a Likert scale in which a score of −6 indicated that symptoms were "a great deal worse," a score of 0 that symptoms were "about the same," and a score of 6 that symptoms were "a very great deal better."

Statistical Analysis

The sample size was calculated to allow two primary comparisons between the groups: the relief of dyspeptic symptoms and healing of gastritis. The significance level was adjusted to 2.5 percent for each comparison with the Bonferroni correction.[15] The assumed rate of treatment success was 40 percent in the group assigned to receive omeprazole and antibiotics and 20 percent in the group assigned to receive omeprazole alone. With the use of a two-sided test and a power of 80 percent for the comparison of dyspeptic symptoms, the study required a total of 320 patients (160 patients in each group), up to 25 percent of whom could be deemed unable to be evaluated. With a sample of this size, the power of the study to detect differences in the rates of healing of gastritis was about 95 percent. The healing rates were assumed to be 50 percent in the group assigned to receive omeprazole and antibiotics and 20 percent in the group assigned to receive omeprazole alone.

The intention-to-treat analyses included all patients who received at least one dose of medication and who were *H. pylori*–positive at entry. In the analyses per protocol, all patients with major deviations from the protocol (use of prohibited drugs before study entry, insufficiently severe symptoms during the run-in period, abnormal findings on pre-entry endoscopy, and history of peptic ulcer disease) were excluded. For the predetermined primary evaluation, treatment was considered successful if a patient reported no symptoms or no more than minimal pain or discomfort centered in the upper abdomen during any of the 7 days preceding the 12-month visit (a score of 0 or 1) on the daily diary cards. The other main response variable was healing of gastritis. Treatment success and healing of gastritis were compared between groups with a Mantel–Haenszel test[16] stratified according to country. The effects of the countries were assessed with the Breslow–Day test.[16] The proportion of patients in whom *H. pylori* infection was eradicated was estimated, and values are given with 95 percent confidence intervals. The quality-of-life scores were compared between the two groups with the use of analysis of variance, with base-line scores included as a covariate.

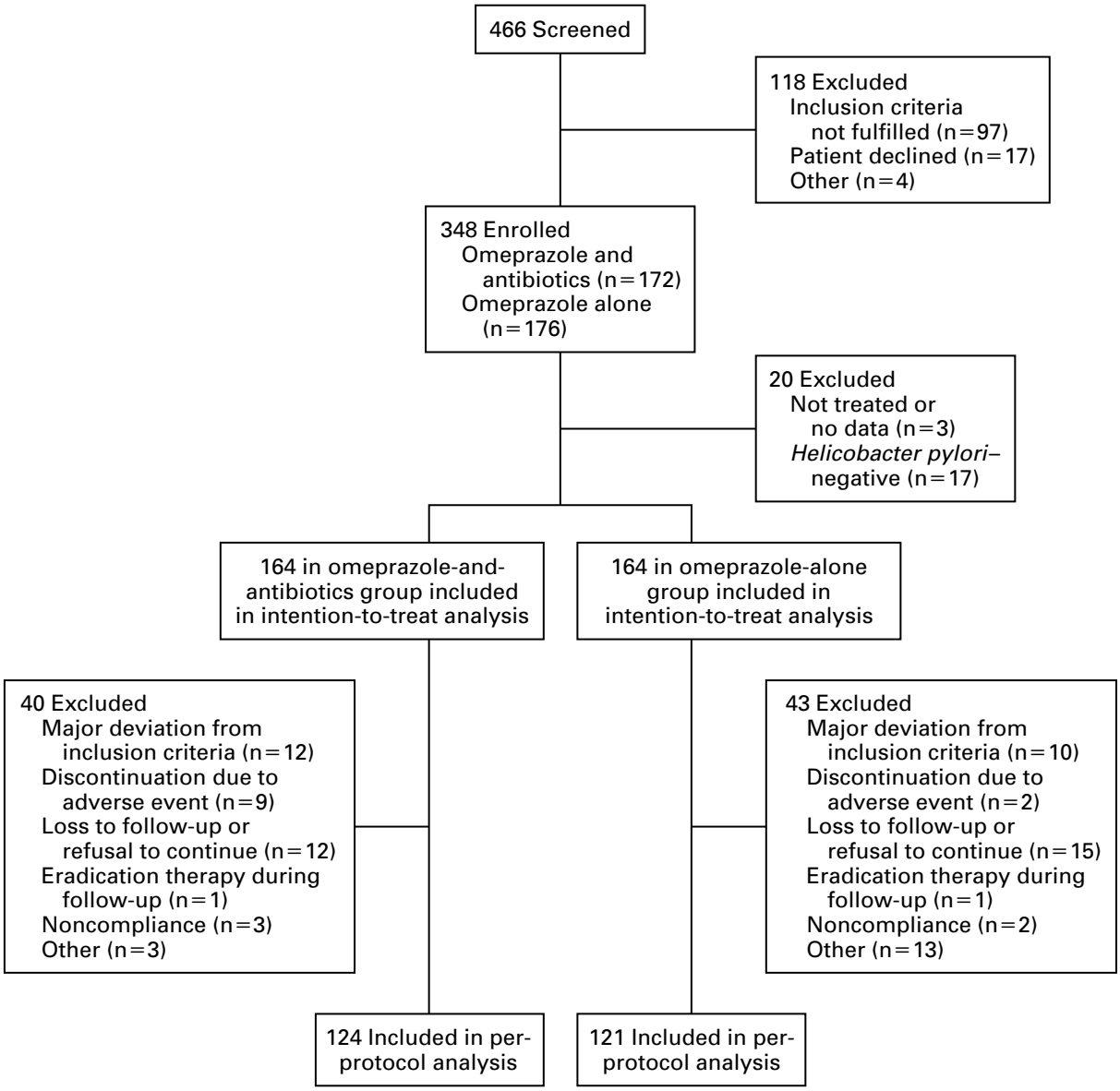


Figure 1. Numbers of Patients Enrolled in the Study and Analyzed According to the Intention to Treat or per Protocol.

RESULTS

Patient Population

We screened 466 patients and excluded 118. Of the 348 patients who were randomly assigned to a treatment group, 328 were included in the intention-to-treat analysis and 245 were included in the per-protocol analysis (Fig. 1). The reasons for exclusion from the analyses are given in Figure 1. The baseline characteristics of the two treatment groups were similar (Table 1).

Treatment Success and Healing of Gastritis

The rates of treatment success and healing of gastritis are given in Table 2. The rates of treatment success were similar in the group given omeprazole, amoxicillin, and clarithromycin and the group given omeprazole alone whether they were analyzed according to the intention to treat (27.4 percent vs. 20.7 percent; absolute difference between groups, 6.7 percent; 95 percent confidence interval, −2.6 to 16.0) or per protocol (28.2 percent vs. 24.0 percent; absolute difference between groups, 4.3 percent; 95 percent confidence interval, −6.8 to 15.3). A Breslow–Day test showed no indication of any inhomogeneity in the results according to the country in which patients were treated ($P>0.7$) in either analysis.

The proportions of patients with no symptoms or minimal symptoms (as recorded on the diary cards)

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 328 PATIENTS INCLUDED IN THE INTENTION-TO-TREAT ANALYSIS.

CHARACTERISTIC	OMEPRAZOLE AND ANTIBIOTICS (N=164)	OMEPRAZOLE ALONE (N=164)
Age (yr)		
Mean	47	47
Range	18–79	19–76
Sex (M/F)	65/99	71/93
Mean weight (kg)		
Men	78	76
Women	66	68
White race (%)	87	88
Smoking status (%)*		
Current smoker	30	27
Former smoker	21	18
Daily alcohol use (%)	46	42
Duration of dyspepsia >1 yr (%)	79	84

*Subjects were asked whether they smoked daily.

during the 7 days before each visit at 6, 9, or 12 months were not significantly different between the two groups whether the data for each time point were analyzed separately or together (13 percent in the group given omeprazole and antibiotics and 10 percent in the group given omeprazole alone; P=0.61 by two-sided Fisher's exact test). Similarly, when the mean symptom scores (Fig. 2) for the visits at 6, 9, and 12 months were compared, there was no significant difference between groups (1.73 in the group given omeprazole and antibiotics and 1.74 in the group given omeprazole alone; P=0.9).

The proportion of patients without gastritis at 12 months was significantly higher in the group given omeprazole and antibiotics than in the group given omeprazole alone (75.0 percent vs. 3.0 percent; P<0.001, according to the intention-to-treat analysis) (Table 2). The results were similar when the data were analyzed per protocol (Table 2).

Quality of Life

In both groups, the patients' quality of life improved after treatment, but not significantly. Overall, the mean scores for the Psychological General Well-Being Index (Fig. 3) and the Gastrointestinal Symptom Rating Scale (data not shown) improved, but there were no significant differences between groups whether the data were analyzed separately for each portion of the scale or for the total score. With respect to the overall effect of treatment, two thirds of the patients in each group reported an improvement in symptoms; the other third indicated that they felt about the same as they had at entry.

Eradication of *H. pylori* Infection

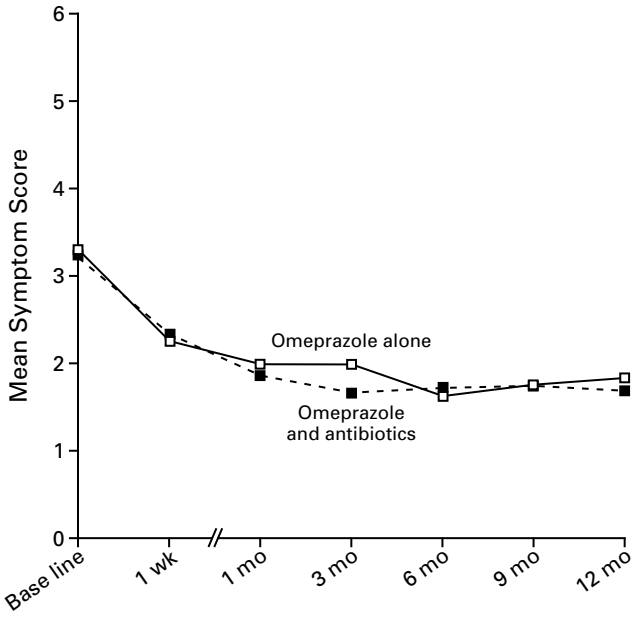
According to the intention-to-treat analysis, *H. pylori* infection was eradicated in 79 percent (95 percent confidence interval, 72 to 85 percent) of the patients in the group given omeprazole and antibiotics (because of missing data, the outcome was unknown for 9 percent) and 2 percent (95 percent confidence interval, 1 to 7 percent) of the patients in the group given omeprazole alone (the outcome was unknown for 10 percent). In the group given omeprazole and antibiotics, 31 percent of those who were cured had relief of symptoms, as compared with 26 percent of those who remained *H. pylori*–positive. According to the analysis per protocol, which excluded patients for whom the outcome was unknown, *H. pylori* infection was eradicated in 87 percent of the patients (108 of 124) in the group given omeprazole and antibiotics.

TABLE 2. RATES OF SUCCESSFUL TREATMENT AND HEALING OF GASTRITIS, ACCORDING TO THE INTENTION-TO-TREAT ANALYSIS AND ANALYSIS PER PROTOCOL.

VARIABLE	OMEPRAZOLE AND ANTIBIOTICS	OMEPRAZOLE ALONE	ABSOLUTE DIFFERENCE BETWEEN GROUPS (95% CI)*	P VALUE
	% (no. of patients/total no.)		%	
Intention-to-treat analysis				
Treatment success	27.4 (45/164)	20.7 (34/164)	6.7 (−2.6 to 16.0)	0.17
Healing of gastritis†	75.0 (123/164)	3.0 (5/164)	72.0 (64.8 to 79.1)	<0.001
Per-protocol analysis				
Treatment success	28.2 (35/124)	24.0 (29/121)	4.3 (−6.8 to 15.3)	0.45
Healing of gastritis	82.0 (100/122)	3.4 (4/117)	78.5 (70.8 to 86.3)	<0.001

*CI denotes confidence interval.

†Data on biopsy assessments were missing for 36 patients, 16 in the group given omeprazole and antibiotics and 20 in the group given omeprazole alone.



	Base line	1 wk	1 mo	3 mo	6 mo	9 mo	12 mo
Omeprazole and antibiotics							
Mean (±SE) score	3.2±0.1	2.3±0.1	1.9±0.1	1.7±0.1	1.7±0.1	1.8±0.1	1.7±0.1
No. of patients	164	161	154	146	142	139	136
Omeprazole alone							
Mean (±SE) score	3.3±0.1	2.3±0.1	2.0±0.1	2.0±0.1	1.6±0.1	1.8±0.1	1.8±0.1
No. of patients	164	163	157	143	133	134	128

Figure 2. Mean Symptom Scores during the Seven-Day Run-in Period (Base Line) and during the Seven Days before Each Follow-up Clinic Visit.

Patients were given diary cards and asked to evaluate their dyspeptic symptoms. A score of 0 indicates the absence of symptoms, and a score of 6 the presence of very severe symptoms. Treatment success was defined as a score of 0 or 1.

Relation among Healing of Gastritis, Eradication of Infection, and Treatment Success

In the group given omeprazole and antibiotics, 119 of the patients had healing of gastritis and eradication of *H. pylori* infection. The rate of treatment success in this subgroup was 30 percent, as compared with a rate of 29 percent among the 14 patients in whom gastritis did not resolve and *H. pylori* was not eradicated. The remaining 31 patients in this group had either healing of gastritis or eradication of *H. pylori* infection, but not both, or had data missing. In the group given omeprazole alone, 137 of the patients remained positive for *H. pylori* and had unhealed gastritis. The rate of treatment success in this subgroup was 23 percent, as compared with a rate of 0 percent among the three patients with resolution of gastritis and eradication of infection. The remaining 24 patients in this group had either healing of gastritis or eradication of *H. pylori* infection, but not both, or had data missing.

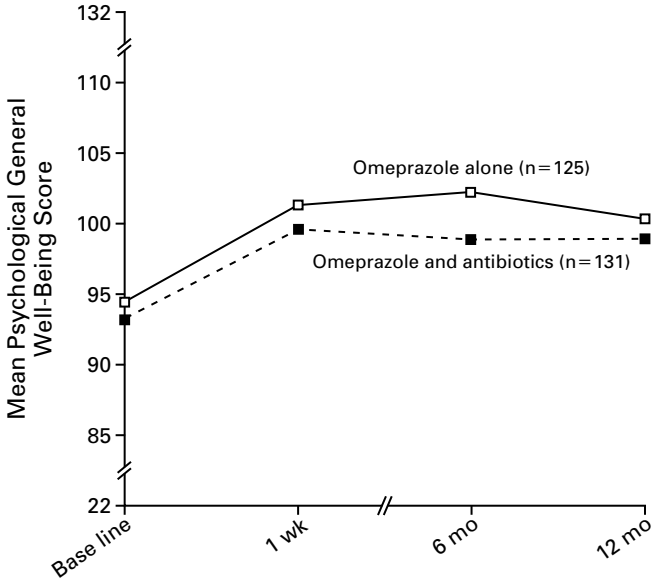
At the 12-month follow-up visits, 11 patients in the group given omeprazole and antibiotics had lesions (10 had erosive esophagitis and 1 had a gastric ulcer), as compared with 9 patients in the group given omeprazole alone (3 had erosive esophagitis, 4 had gastric ulcers, and 2 had duodenal ulcers).

Evaluation of Safety

Safety data were available for 169 patients in the group given omeprazole and antibiotics and 176 patients in the group given omeprazole alone. There were no serious adverse events in either group during treatment. Few patients had treatment stopped because of an adverse event: 12 in the group given omeprazole and antibiotics and 2 in the group given omeprazole alone. The most common adverse event, diarrhea, occurred in 63 patients in the group given omeprazole and antibiotics and in 10 patients in the group given omeprazole alone.

DISCUSSION

Peptic ulcer disease is strongly associated with *H. pylori* infection. The eradication of this infection prevents relapse of gastric and duodenal ulcers, unless reinfection occurs or patients take ulcerogenic drugs such as nonsteroidal antiinflammatory drugs.[17,18]



MEAN ±SE				
Omeprazole and antibiotics	93.1±1.6	99.6±1.5	98.9±1.6	99.0±1.7
Omeprazole alone	94.4±1.4	101.3±1.4	102.3±1.5	100.4±1.4

Figure 3. Mean Scores for the Psychological General Well-Being Index at Base Line and after Treatment with Omeprazole and Antibiotics or Omeprazole Alone.

The Psychological General Well-Being Index was used to assess the patients' quality of life. On this scale, the worst possible score is 22, and the best possible is 132.

A role for *H. pylori* in nonulcer dyspepsia also seems plausible, and numerous studies have investigated a possible link. However, the results of clinical trials have so far been equivocal, and the role of *H. pylori* remains highly controversial.[7,19,20] In a recent critique of 16 therapeutic trials in patients with nonulcer dyspepsia who had *H. pylori* infection,[21] all of the studies were considered to have at least one serious methodologic weakness. Our study guidelines were drawn up after a systematic review of trial methods.[22]

We used a strict definition of nonulcer dyspepsia,[6] since this was one of the major variants in previous studies. It can be argued that if the entry criteria are too strict, the study group is not truly representative of people with dyspepsia, but the use of more relaxed criteria may result in the inclusion of patients with other gastrointestinal diseases, such as gastroesophageal reflux disease and peptic ulcer disease. The inclusion of patients with gastroesophageal reflux disease may decrease the chance of a positive response, whereas the inclusion of patients with peptic ulcer disease may increase the chance of a positive response.

We based our sample size on careful predictions of efficacy and included a 12-month period of follow-up, which is sufficient time to allow healing of gastritis.[9] *H. pylori* infection was detected with the use of validated methods[11,12] and treated optimally with omeprazole, amoxicillin, and clarithromycin,[23,24] and both patients and physicians were unaware of the patients' *H. pylori* status at follow-up. The rather low rate of eradication of *H. pylori* infection in the intention-to-treat analysis of the group given omeprazole and antibiotics was for the most part accounted for by the relatively large proportion (9 percent) of patients for whom the outcome was unknown.

Studies of nonulcer dyspepsia have often been criticized for failing to use validated outcome measures.[22] We used a stringent definition of treatment success: the absence of symptoms or the presence of only minimal symptoms. As a means of determining the response, we used a Likert scale to assess the severity of symptoms[25,26] as well as the Gastrointestinal Symptom Rating Scale and the Psychological General Well-Being Index, both of which have been validated and widely used in different countries,[13,14,27-29] to assess the patients' quality of life.

There were no significant differences in the rates of symptom relief or other secondary variables between the two treatment groups during the 12 months of follow-up, and there was also no apparent difference in the rates of treatment success between patients in whom gastritis had healed and *H. pylori* was eradicated and those with persistent gastritis and infection. Although the quality of life after treatment

did not differ significantly between the two groups, both groups had a marked improvement in all the variables analyzed in this assessment, including the severity of dyspeptic symptoms, as reported previously in many other studies.[21,30,31] This finding confirms that we used sensitive instruments of assessment.

In studies of nonulcer dyspepsia, the use of repeated endoscopy is important to rule out the possibility of a high incidence of ulcers at follow-up. In our study, fewer than 3 percent of patients had peptic ulcers at follow-up and all but one of the ulcers occurred in patients with persistent *H. pylori* infection. These results suggest that we did not include patients who had peptic ulcer disease but had no evidence of it on endoscopy and instead included only patients with non-ulcer dyspepsia. We conclude that although the eradication of *H. pylori* infection may help prevent or cure peptic ulcer disease, it is not likely to have a major role in the treatment of symptoms in patients with nonulcer dyspepsia.

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APPENDIX

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