A Randomized Controlled Trial of an Enhanced Patient Compliance Program for *Helicobacter pylori* Therapy

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**Objectives:** To determine whether an enhanced compliance program (ECP) improves patient compliance with bismuth subsalicylate, metronidazole, and tetracycline hydrochloride (BMT) triple therapy for the treatment of *Helicobacter pylori* infection and to identify factors that affect compliance with therapy.

**Design:** A randomized controlled trial conducted in 4 staff-model health centers of a health maintenance organization in Massachusetts.

**Patients and Methods:** A total of 125 patients 18 years of age or older with peptic ulcer disease or dyspepsia whose clinicians prescribed BMT triple therapy for 14 days were randomized to a control group or to the ECP group. The ECP group received medication counseling (written and oral) from a pharmacist, along with a medication calendar and a minipillbox, as well as a follow-up telephone call after initiation of therapy. Compliance was assessed by a pill count, and factors affecting adherence to the regimen were identified by patients’ reports.

**Results:** There was no statistically significant difference between the 2 groups in the number of patients taking more than 60% of the medications (89% of the control group vs 95% of the ECP group; *P* > .30). However, there was a statistically significant difference in the number of patients taking more than 90% of the medications (67% of the control group vs 89% of the ECP group; *P* < .01). An intention-to-treat analysis confirmed these results. The most frequently reported adverse effect was gastrointestinal intolerance. Other factors reported to affect compliance included the frequency of dosing and the number of pills.

**Conclusions:** These findings suggest that although adverse effects were common, most patients were able to complete 60% or more of the 2-week regimen. An ECP further improved the percentage of medications taken.

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Helicobacter pylori plays a major role in peptic ulcer disease. Clinical data have demonstrated that eradication of *H pylori* significantly reduces gastric and duodenal ulcer recurrence rates. The role of *H pylori* in nonulcer dyspepsia remains controversial owing to the lack of well-designed clinical trials addressing this issue. Although practice guidelines have been developed for the treatment of peptic ulcer disease, with an emphasis on eradicating *H pylori*, there is no consensus regarding the optimal regimen for patients with *H pylori* infection. Two weeks of triple therapy consisting of a bismuth compound (bismuth subsalicylate), metronidazole, and tetracycline hydrochloride (BMT) appears to produce consistent, high eradication rates and has been viewed as one of the preferred *H pylori* regimens. (The treatment of active duodenal ulcers using bismuth subsalicylate, tetracycline, and metronidazole is patented and commercially available in a compliance kit [Helidac Therapy; Procter & Gamble Pharmaceuticals Inc, Cincinnati, Ohio]. Helidac Therapy is indicated for use in conjunction with a histamine, antagonist.) However, many clinicians are discouraged by the frequency of adverse effects and the complexity of the dosing schedule. Graham et al investigated the factors influencing the efficacy of bismuth-based triple therapy and found that *H pylori* organisms were eradicated in 96% of the patients who took 60% or more of their medications but in only 69% of the patients who took less than 60% of their medications. If medication adherence could be enhanced, the clinical effectiveness of bismuth-based triple therapy might be increased. (In this article, we use adherence and compliance interchangeably, although we recognize that compliance may be interpreted as placing the patient in a passive role, whereas adherence emphasizes a patient’s active role in working with a health provider on achieving a common goal.) Adherence to medical recommendations is a major challenge for both patients and their clinicians, and is prob-
 PATIENTS AND METHODS

The study was a prospective, randomized controlled trial that was conducted at 4 ambulatory health centers of Harvard Pilgrim Health Care, a managed-care organization in New England. The protocol was approved by the institutional review board of Harvard Pilgrim Health Care. Patients were eligible for the study if they were 18 years of age or older, were English speaking, had been seen by a gastroenterologist or internist, had evidence of *H pylori* infection, and had a diagnosis of peptic ulcer disease or dyspepsia, and if their clinician had prescribed 2 weeks of BMT therapy. The diagnosis of peptic ulcer disease or dyspepsia was made by the patient’s clinician. The diagnosis of *H pylori* infection was based on serologic test results (Pylori ELISA II; BioWhittaker Inc, Walkerville, Md, or Premier H pylori; Meridian Diagnostics Inc, Cincinatti, Ohio). Findings of histological examination, or a positive biopsy rapid urease test result. Patients were excluded from the study if they were pregnant, allergic to any of the study medications, had received prior treatment for *H pylori* infection, had undergone recent treatment (<1 month) with any of the study medications, had received previous metronidazole therapy, or did not have a telephone. Potential participants were identified by the health center pharmacists when they filled their triple therapy (BMT) prescriptions.

Patients were randomized at each health center by the study pharmacists to either the control group or the ECP (intervention) group by means of sealed envelopes. A stratified blocked randomization was used to minimize variation due to chance. The study cohort was separated at baseline into patients with peptic ulcer disease and patients with dyspepsia, and then randomized in blocks of 4 within each of the 2 strata. Patients who participated in the study were given 2 coupons for subsequent prescriptions to be filled at the health centers’ pharmacies.

All patients enrolled in the study received 2 weeks of triple therapy consisting of 2 bismuth subsalicylate chewable tablets to be taken 4 times daily, 230-mg metronidazole tablets to be taken 3 times daily, and 500-mg tetracycline hydrochloride capsules to be taken 4 times daily.

Patients in the ECP group received initial counseling by the pharmacist, which typically lasted 10 to 15 minutes and included discussion of BMT triple therapy and *H pylori* infection. Written information on *H pylori* infection and the importance of compliance with the regimen was also provided. The pharmacist taught the patient to check off on a pocket-sized medication calendar every dose of medication taken. The pharmacist also taught the patient to put the correct daily doses in a pocket-sized pillbox that holds a 1-day supply of medication. Follow-up telephone calls were made by the pharmacist at least 3 days after the initiation of therapy to ensure that the patient was tolerating the medications and was taking the medication appropriately. Pharmacists were instructed to record any adverse effects reported by the patient. Additional counseling was given over the telephone when needed. On filling the prescriptions, patients who were assigned to the control group received the standard instructions on how to take the prescribed medications, along with an explanation of precautions and adverse effects. No other compliance aids were provided to the control group.

All patients received a telephone call from the pharmacist at the end of therapy to discuss their experience with the regimen. The pharmacist was given a script outline developed by the investigators to solicit factors that may have affected compliance. The patient was initially asked in an open-ended fashion to describe factors that affected his or her compliance. Also, the pharmacist asked specifically about adverse effects, number of pills taken, and frequency of dosing in those patients who did not provide any specific factors that may have influenced their compliance. The pharmacist also reminded the patients to return their medication bottles to the pharmacy.

The recruitment of patients began in July 1995 and ended in October 1997. The primary study outcomes were the numbers of patients able to complete 60% or more and 90% or more of the 2-week regimen. The percentage of each individual drug taken was measured. The mean of the 3 individual percentages of each drug taken was the final percentage that was recorded. The patients reported all the factors that may have affected their ability to fully comply with the regimen, and these factors were also measured.

Approximately 65% of the patients were able to complete 60% of the triple therapy regimen in a study environment; therefore, we estimated that 60% of patients in a less controlled environment would be able to take 60% of their medications. We considered a 20% improvement in the compliance rate to be clinically significant. Statistical literature, along with a computer program (SSIZE, available from Hsieh14) provided the requisite sample size for the analysis. At a 3% level of significance and 80% power, a total of 112 patients was required.

Data analysis was based on the total number of patients in the control and intervention groups who completed the study, defined as returning to the pharmacy for a pill count. Logistic regression analysis using a commercially available statistical package (Version 6.1 for Windows; SPSS Inc, Chicago, Ill, 1989-1995) was performed to determine if there was a statistically significant difference between the 2 groups. Dichotomous outcomes were used because consumption of 60% or more of the medication was associated with a higher eradication rate in a previous study. Covariates in this analysis included age, sex, occupation, education, severity of pain symptom, first or recurrent episode of symptoms, number of other medications taken during triple therapy, concomitant use of omeprazole or a histamine antagonist, and diagnosis (peptic ulcer disease or dyspepsia). A 2-sided unpaired *t* test to detect statistically significant differences between the mean percentages of medication taken in the 2 groups was also conducted retrospectively.

Two intention-to-treat analyses were also performed. The first analysis assumed that the patients who did not return for a pill count, those in the control group took 100% of the medication and those in the ECP group took 0%. The second analysis assumed that all patients who were unavailable for follow-up did not take any of the medication. *χ*² Tests were used to determine if significant differences existed between the 2 groups regarding factors that influenced compliance.
saking patients about the importance of adherence to the prescribed regimen and reinforcing the message with written instruction have been shown to increase patients’ adherence to a regimen of antibiotics for streptococcal pharyngitis. The impact of increased knowledge of the treated disease on patient compliance is unclear. Sackett et al found that a better understanding of hypertension and its treatment did not improve patient compliance with antihypertensive therapy. However, it is possible that providing disease-specific information might encourage patients to participate in a short course of treatment that will result in long-term benefits.

The objective of our study was to determine whether adherence with a 2-week course of triple therapy (BMT) for H pylori infection could be enhanced through a program composed of education, compliance aids, and close follow-up by a pharmacist.

**RESULTS**

Two hundred twenty-three patients were approached by the study pharmacists to participate in the study. Forty-five patients declined; the main reason (62%) stated was the lack of time to participate. Fifty-three patients did not meet the eligibility criteria. The reasons for exclusion were a history of metronidazole treatment (n = 19), recent treatment with one of the study medications (n = 2), previous treatment for H pylori infection (n = 12), non–English speaking (n = 17), and allergy to salicylate (n = 3). A total of 125 patients were enrolled in the study. Sixty-three patients had a diagnosis of peptic ulcer disease, and 62 patients had a diagnosis of dyspepsia. Sixty-two patients were assigned to the ECP group (26 patients with peptic ulcer disease and 36 patients with dyspepsia). Sixty-three patients were assigned to the control group (23 patients with peptic ulcer disease and 40 patients with dyspepsia) (Table). Nine patients were unavailable for follow-up: 8 were in the control group and 1 was in the ECP group (Fisher exact test, P<.05). Of those who finished the study, 95% (58/61) of patients in the ECP group and 89% (49/55) of patients in the control group completed 60% or more of the regimen (P>.30). Eighty-nine percent (54/61) of patients in the ECP group and 67% (37/55) of patients in the control group achieved a 90% level of compliance (P<.01) (Figure 1). Adjustment by logistic-regression analysis did not alter the results of the study. When the mean percentage of medication taken was evaluated as a continuous variable using a 2-sided unpaired t test, there was a statistically significant difference between the 2 groups (94% of the ECP group vs 87% of the control group; P<.05).

The first intention-to-treat analysis conducted under the assumption that those in the control group who were unavailable for follow-up had completed 100% of the regimen and those in the ECP group had completed 0% confirmed the above results, showing no statistically significant difference in the number of patients who completed 60% or more of the regimen (94% of the ECP group vs 90% of the control group; P>.72). There was still a statistically significant difference in the number of patients taking 90% or more of the medication (87% of the ECP group vs 71% of the control group; P<.05). With the second intention-to-treat analysis assuming that all patients who were unavailable for follow-up took 0% of the medication, the results were as follows: 94% of the ECP group and 78% of the control group took 60% or more (P<.05) of the medication; 87% of the ECP group and 59% of the control group took 90% or more (P<.01) of the medication.

A total of 125 patients were contacted, and 120 patients (96%) were available to comment on factors that they felt affected their compliance (5 patients were unavailable for follow-up before the telephone interview). Four patients provided information on these factors but did not return for a pill count. Thirty-six percent (43/120) of the patients had experienced some form of gastrointestinal intolerance, including nausea, vomiting, diarrhea, stomach cramps, and constipation. Twenty percent (24/120) of the patients complained of taste disturbance, especially with metronidazole. Twenty-six percent (31/120) of the patients felt that the frequency of dosing had affected their ability to comply with the regimen, while 22% (26/120) of the patients suggested that the number of pills also affected their compliance. Twenty-two percent of patients experienced...
other adverse effects such as dry mouth, headache, and drowsiness (Figure 2). There were no differences between the 2 groups in the number of patients complaining of gastrointestinal intolerance, taste disturbance, number of pills, and miscellaneous adverse effects. Frequency of dosing, however, was less often mentioned as a complaint in the ECP group ($\chi^2$, P<.05). Nine (8%) of the 116 patients who completed the study had a compliance rate below 60%. Seven of these patients attributed the low compliance rate to the intolerable adverse effects. One patient complained of the frequency of dosing in addition to the adverse effects; another patient felt that the number of pills and frequency were the contributing factors.

When the patients assigned to the ECP group were asked to comment on what part of the intervention was most helpful, 31% (19/61) of the patients suggested the combination of either pharmacist education and pillbox or pillbox and calendar. Overall, the pillbox was mentioned 35 times, the calendar 21 times, and the counseling by the pharmacist 19 times.

Understanding the causes of noncompliance and identifying methods to assist patients to follow their regimens may improve health care outcomes. The health decision model suggests that noncompliant behavior is multifactorial. By modifying general and specific health beliefs, tailoring the regimen to reflect patient preferences, modifying the patients' attitudes toward the therapeutic regimen, enhancing knowledge, and modifying social interaction factors, compliance can be improved. Our ECP is focused specifically on enhancing the patients' attitudes toward treatment regimens and their knowledge about their disease and medications, as well as providing them with tools such as pillboxes and medication calendars to enhance the administration process. Pharmacists clearly have a role within the model in enhancing patient compliance.

One criticism raised with regard to compliance trials is that interventions are frequently provided by an experienced research staff that may not be available in the actual clinical setting. When we initiated this clinical trial, we did not use research staff to recruit potential participants; staff pharmacists were asked to take on the additional responsibility. This approach allowed us to determine the feasibility of an ECP in an ambulatory care setting in which resources are scarce. We were faced with an unexpectedly low enrollment rate in 2 of the pharmacies. This low rate was mainly attributable to the lack of an adequate pharmacy staff to support the program. Some patients were not willing to participate after spending time in the physician's office and the pharmacy. It would have been more efficient if a pharmacist had been available to recruit patients while their prescriptions were being filled.

We used BMT triple therapy as our study regimen for several reasons. Although complicated, it is effective and inexpensive, and it is the only regimen that has shown a correlation between the rate of successful eradication and the percentage of medication taken. A pill count was used as the primary measure of compliance. We recognize that it is not an optimal tool. Some patients may discard tablets if they know that a pill count is being used to measure their compliance. Additionally, a pill count does not define exactly when pill consumption began, or whether periods of overcompliance and undercompliance canceled each other out. However, it is a simple and inexpensive method. Other sophisticated monitoring devices, such as an electronic monitoring device that attaches to the original container, may not be appropriate when daily medications are transferred to a pocket-sized pillbox. Furthermore, a pill count was used in the previous study that demonstrated a correlation between percentage of medication taken and rate of successful H pylori eradication. To minimize sensitizing patients, pharmacists were instructed not to explicitly tell patients that returning the medication bottles with any unused medications was for the purpose of a pill count.

We found that the majority of patients in both groups were able to take more than 60% (95% of the ECP group vs 89% of the control group) of the prescribed medication. There was no statistically significant difference between the 2 groups ($P > .30$). We did not anticipate such a high compliance rate in the control group, given the general impression that BMT therapy was overly complicated and frequently intolerable. Many factors could have affected the compliance rate in both groups. The awareness of the potential problems with BMT therapy may have prompted physicians to provide more counseling to their patients. Any compliance measurement may bias results by alerting patients that their behavior is being monitored. Also, one may question whether patients who are motivated to participate in a study are truly representative of the general population, since they may be more willing to comply with the regimen. To minimize some of these potential biases, we instructed our pharmacists to emphasize to potential participants that the goal of the study was to determine the practicality of the regimen, not their ability to be compliant. We also provided a small incentive (providing coupons for subsequent prescriptions filled at the pharmacy) to attract patients who might otherwise decline to participate.
The observation that a high percentage of patients can comply with the BMT regimen may not be true if we assume that all patients who were unavailable for follow-up were noncompliant. This assumption will result in a poor compliance rate of 14% (18/125) instead of the 8% (9/116) rate that was observed in patients who completed the study. Interestingly, such an assumption will further support an ECP, since the second intention-to-treat analysis demonstrated that the percentage of patients in the ECP group who completed 60% or more of the medication was significantly higher than in the control group (94% of the ECP group vs 78% of the control group; P<.05). The large number (20%, 45/223) of patients who declined to participate may limit the generalizability of our results to unselected clinical populations, since these patients might be less likely to comply with any structured directions.

The difference between the 2 groups in the number of patients who completed 90% or more of the regimen is statistically significant even when analyzed under the intention-to-treat method favoring the control group (P<.05). These findings suggest that the ECP is beneficial when compliance is defined as 90% or more of medications taken. Based on a previous bismuth-based H pylori regimen study,2 completion of 60% or more of the medication will achieve a desirable outcome. Among patients completing our study, we did not find that the ECP increased the proportion of patients who achieved compliance at the 60% or greater level. Therefore, allocating resources to develop a comprehensive compliance program may not be cost-effective for this particular regimen. On the other hand, the second intention-to-treat method, which assumed that all the patients who were unavailable for follow-up were less compliant, implies that an ECP may still be useful. There is limited information on the desirable amount of medication required for other regimens or conditions. In those cases, one may need to aim for a higher percentage of medication taken, and the ECP may then be valuable. The benefit of this ECP cannot be extrapolated to long-term treatment since the therapy studied was a short-term regimen. Haynes et al20 suggest that as the number of effective self-administered treatments continues to expand, helping patients adhere to their medical treatments may have far greater effects on health than any treatment itself. Therefore, it may be important to develop and support initiatives to improve patient compliance.

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