Proton pump inhibitors (PPIs) represent a landmark development in gastroenterology. These drugs irreversibly inhibit the gastric H+, K+ ATPase pump and reduce both basal and stimulated gastric acid output. Presently, five PPIs are marketed in the U.S.: omeprazole (Prilosec, AstraZeneca), lansoprazole (Prevacid, TAP Pharmaceuticals), rabeprazole (AcipHex, Eisai Inc.), pantoprazole (Protonix, Wyeth-Ayerst) and esomeprazole (Nexium, AstraZeneca); the latter two were approved most recently. PPIs are efficacious and cost-effective for the treatment of severe gastroesophageal reflux and other acid-related illnesses.1,2 Prescriptions for PPIs have increased dramatically over the last decade,3 and available drug utilization data from Australia and the United Kingdom indicate widespread use of PPIs for indications such as non-ulcer dyspepsia that are outside current prescribing guidelines.3-5 There are limited data, however, on how patients actually use PPIs, and on the frequency of breakthrough symptoms during therapy. The present study was undertaken to provide information on self-reported PPI medication-usage patterns and to evaluate the occurrence and management of acid-breakthrough symptoms.

OBJECTIVE
The objective of this study was to gain a better understanding of attitudes toward PPIs and usage patterns of these agents in individuals prescribed these drugs for acid-related illnesses. A specific focus of this study was to characterize apparent acid breakthrough symptoms among PPI users and to determine the self-management of such symptoms.

METHODS
Adults (≥18 years of age) prescribed PPIs were targeted for evaluation. A sample was randomly selected nationwide from postal zip codes of households returning health questionnaires (Polk Research) in which any family member reported current use of omeprazole or lansoprazole (the then-available prescription PPIs). An attempt was made to obtain a representative sample of PPI users in terms of gender, age distribution, and prescribed medication based on 1999 PPI retail sales (January–October) and NDTI (National Disease and Therapeutic Index) data.

To be included in this study, individuals must have reported PPI medication-usage patterns and to evaluate the occurrence and management of acid-breakthrough symptoms. A total of 400 persons qualified as PPI users for this study and were interviewed by telephone between February 4 and 13, 2001, after providing verbal consent. Key elements of the questionnaire are shown in Figure 1. The individuals were queried about their PPI usage patterns, the occurrence of breakthrough acid-related symptoms, and the use of supplemental acid-relief remedies. Each survey took approximately 15 minutes to complete, and respondents received no financial remuneration for their participation.
Figure 1. Key Elements of Questionnaire*

(1a) About how often do you use (Prilosec/Prevacid) for stomach problems?
   1. Every day
   2. 4 to 6 days per week
   3. 2 to 3 days per week
   4. Once a week/weekly
   5. Less often than once a week

(1b) Thinking about the days when you use it, about how many times a day do you take (Prilosec/Prevacid) for these problems?
   1. Once a day
   2. Twice a day
   3. Three or more times a day

(1c) And how often did your doctor tell you to take it?
   1. Once a day
   2. Twice a day
   3. Three or more times a day
   4. Use as needed
   5. Other

(2a) Do you usually use (Prilosec/Prevacid):
   1. Only before your symptoms start,
   2. Only after your symptoms start, or
   3. Sometimes before and sometimes after?

(2b) Do you typically take (Prilosec/Prevacid) at the same time of day? (Yes or No)

(2c) What time or times of day do you typically take (Prilosec/Prevacid)?
   1. Morning
   2. Luncheon
   3. Afternoon
   4. Dinnertime
   5. Evening (after dinner)
   6. At bedtime
   7. During the night (after bedtime)

(3a) Thinking about the days when you take (Prilosec/Prevacid), are there ever any of those days when you still have some heartburn, acid indigestion, reflux or other stomach problems? (Yes or No.) Let’s call these breakthrough symptoms.

(3b) Thinking about the last 10 days that you took (Prilosec/Prevacid), on about how many of those days did you experience breakthrough symptoms after you took (Prilosec/Prevacid)?

(3c) What time or times of day do you typically experience breakthrough symptoms?

(3d) At which of those times do you experience breakthrough symptoms most often?

(4a) Please tell me what percent of the time you do each of these things when you have breakthrough symptoms.
   1. Take a nonprescription stomach remedy
   2. Take another (Prilosec/Prevacid) pill
   3. Just do nothing - you deal with the symptoms
   4. Do something else (specify)

(4b) Did someone recommend that you take a nonprescription stomach remedy when you experience breakthrough symptoms? (Yes or No)

(4c) Thinking about the times you suffer breakthrough symptoms, over the past month what brand or brands of nonprescription stomach remedies have you used for breakthrough symptoms on days when you take (Prilosec/Prevacid)?

(5) For what condition or conditions did the doctor prescribe (Prilosec/Prevacid)?
   1. Heartburn/burning feeling in chest
   2. Reflux/acid reflux
   3. Acid indigestion/acid in stomach
   4. Upset stomach
   5. Stomach or intestinal cramps or pain
   6. Hiatal hernia
   7. Ulcer
   8. GERD/Gastroesophageal Reflux Disease
   9. Acid feeling in throat
   10. Other Stomach ailments (Specify)

(6) How satisfied are you with (Prilosec/Prevacid). Use a 0-10 scale where “10” means you are extremely satisfied and “0” means you are not at all satisfied.

(7a) Since you started taking (Prilosec/Prevacid), have you ever taken any nonprescription stomach remedies such as antacids or acid reducers? (Yes or No)

(7b) About how often do you, yourself, use a nonprescription stomach remedy for problems such as heartburn, acid indigestion, reflux, or problems such as ulcers or hiatal hernias?
   1. Everyday/daily
   2. 2 to 6 times per week
   3. Once a week/weekly
   4. 2 to 3 times a month
   5. Once a month
   6. Less often than once a month

(8) Do you ever take a nonprescription stomach remedy and (Prilosec/Prevacid) during the same day? (Yes or No)

(9) How safe do you feel it is to take both (Prilosec/Prevacid) and a nonprescription stomach remedy in the same day.
   Please use the same 0 to 10 scale where “10” means you feel that it is extremely safe and “0” means you feel it is not safe at all.

*These questions were extracted from the script used by the telephone interviewers. Demographic questions were excluded from this Appendix.
RESULTS
The individuals interviewed in this study were representative of the target population of PPI users in terms of age (median, 56 years), gender (59% female) and prescribed PPI (67% omeprazole), as shown in Table 1. Our respondents described the most common reason for their PPI use as being either “reflux” (51%) or heartburn (28%).

Pattern of PPI Usage
Table 2 summarizes the PPI usage pattern reported by respondents. The average omeprazole user among our sample had been taking this PPI for three years (mean, 35.2 months), whereas the average lansoprazole duration of use was two years (mean, 23 months). Fewer than 15% of survey respondents (13.5%) had been taking PPIs for less than six months. All had used PPI therapy at least once per week. In fact, 84% of the study sample reported daily PPI use, with only 4% reporting the use of a PPI only once per week. Of note, 97% of the respondents indicated that their doctors had instructed them to take their PPIs daily, indicating that a significant minority (approximately 13%) had opted for ‘on-demand’ therapy rather than complying with the prescribed PPI regimen. On days when they used a PPI, most respondents reported taking the drug once daily (89%), and the majority (71%) reported routinely taking their PPIs before the onset of symptoms. Only 9% of our sample reported taking their PPIs only after symptoms presented. Nine of ten (90%) respondents indicated that they typically took their PPIs at the same time of day, with morning being the most popular time (72%).

Breakthrough Symptoms
Acid-breakthrough symptoms—defined as heartburn, acid indigestion, reflux, or other stomach problems—were common among our sample of PPI users, with 44% of respondents indicating that they had experienced such symptoms on days when they took their PPIs. Of 175 individuals reporting acid-breakthrough symptoms, such symptoms were reported on 28% of the days that PPIs were taken. Among respondents taking a PPI daily, acid breakthrough symptoms were experienced by 46% and occurred on 28% of the treatment days.

Acid-breakthrough symptoms tended to occur most commonly in the evening after dinner and at night (Figure 2). Nearly one-half (48%) of our total cohort reported that these symptoms interrupted their sleep; among these individuals, the average frequency of waking up was once every 3.5 nights, or twice per week.

Over-the-counter (OTC) stomach remedies were used for these acid breakthrough symptoms about half of the time. In this setting, the use of an additional PPI capsule occurred only about 5% of the time (Figure 3). Antacids were the most common OTC remedy taken to treat acid-breakthrough symptoms (Figure 2). Two-thirds (65%) of respondents who reported using OTC stomach remedies for acid-breakthrough symptoms added these medications to their PPI therapy without the knowledge of their physicians.
For those respondents who did not use OTC stomach remedies conjointly with their PPIs, their explanations focused on concerns over mixing medicines (23%).

**Satisfaction with PPIs**
Respondents were asked to rate their level of satisfaction with their PPIs on a scale of 0 (not at all satisfied) to 10 (extremely satisfied). Overall, 59% of the 400 respondents indicated that they were extremely satisfied with their PPIs. The number of respondents rating extreme satisfaction with their PPIs declined to 34% among the subset of individuals experiencing acid-breakthrough symptoms.

**Concomitant Medication Use**
Respondents were queried about their use of OTC stomach remedies irrespective of whether they experienced acid-breakthrough symptoms. Nearly one-half (n=179, 45%) of PPI users in this study reported having taken an OTC stomach remedy since they began using a PPI and within the past year; of these, 82% reported ever taking a PPI and OTC remedy on the same day. The gender and age distributions of these dual PPI/OTC users were nearly identical to those for the entire sample (61% female; median age of 55 years).

The majority (57%) of dual PPI/OTC users indicated that they took OTC products for their stomach ailments at least once per week, with 11% reporting that they needed to supplement their PPIs with OTC medications daily. Dual PPI/OTC users took OTC remedies for an average of 9.5 days per month, or once every three days. Although most (78%) dual PPI/OTC users reported taking an OTC remedy one to two times per day (on the days of OTC remedy use), nearly one-quarter (22%) indicated that they needed to take their OTC medications three or more times daily.

Nearly all respondents (94%) who indicated that they used a PPI and an OTC remedy on the same day did not take the two acid-relief medications at the same time of day. Among this subset of dual PPI/OTC users (n=146), OTC remedies were reportedly taken most often in the evening after dinner (33%) or at night (26%). These times correspond closely to the periods most often associated with acid-breakthrough symptoms (see Figure 2).

All respondents were asked to rate how safe they believed it was to take both a PPI and an OTC stomach remedy on the same day, using an 11-point scale (0=not at all safe; 10=extremely safe). Not surprising, only 8% of dual PPI/OTC users rated this type of concomitant therapy as unsafe (scores of 0 to 4) and 72% assigned it a high rating (8–10). By comparison, 33% of respondents who reported using only a PPI rated the use of a PPI and an OTC stomach remedy on the same day as unsafe (0–4), and only one-quarter gave it a high rating (8–10). More PPI/OTC dual users than PPI-only users (43% vs. 25%) had discussed with their doctor the concomitant use of both medications—which might explain the apparent difference in the perceived safety of this combination.

**DISCUSSION**
Our survey of a representative national sample of PPI users indicates that the majority of individuals taking these drugs for gastric acid-related illnesses appear to be very satisfied with the therapeutic results. Nevertheless, acid-breakthrough symptoms appear to be common among PPI users. Even among compliant individuals taking PPIs daily as directed by their physicians, nearly one-half (46%) experienced acid-breakthrough symptoms. These symptoms tended to occur during 28% of their days of PPI use. Such symptom breakthrough decreased satisfaction with the prescribed PPI therapy. Although such symptoms could occur at any time during the day, acid-breakthrough symptoms seemed most common after dinner and at bedtime or overnight. About one-half of PPI users reported waking up because of acid-breakthrough symptoms; among these individuals, sleep was interrupted by these symptoms an average of twice per week.

The high rate of acid-breakthrough symptoms while on PPI therapy—particularly the frequent occurrence of noctur-
nal breakthroughs—might be explained by insufficient nighttime acid control with PPIs, as demonstrated in several studies.6–8 For example, Katz and colleagues reported that nocturnal acid breakthrough, defined objectively as gastric pH below 4 continuously for more than 60 minutes, occurred in one-third of healthy volunteers receiving a seven-day course of treatment with twice-daily omeprazole 20 mg, and in half of the volunteers receiving a similar course of treatment with twice-daily lansoprazole 30 mg.6 Nocturnal acid breakthrough has been documented in as many as 70% of patients with gastroesophageal reflux on twice-daily PPI therapy2 and in 100% of the participants in one study involving a single morning PPI dose.9

Almost half (44%) of the daily PPI users interviewed in our study took OTC stomach remedies to control their breakthrough symptoms, and most (65%) did so without consulting their physicians. Antacids were the most common type of OTC remedy taken by PPI users to treat acid-breakthrough symptoms. Antacids provide only relatively short-term acid control, which likely contributes to the substantial proportion of dual PPI/OTC users (22%) who reported having to take their OTC medications three or more times daily on those days when they needed an OTC remedy. Longer-term suppression of gastric acid secretion can be achieved by a histamine H₂-receptor antagonist (H₂RA) such as famotidine or ranitidine.10 Several clinical groups have reported that nighttime administration of an H₂RA is effective in controlling nocturnal acid breakthrough, and the effectiveness of bedtime H₂RAs has been shown to be greater than that of even a third dose of a PPI.8,11,12 Only a small proportion (6%) of our cohort of dual PPI/OTC users reported using a H₂RA to treat acid-breakthrough symptoms, so it is not possible to assess the usage patterns or the success of this form of OTC stomach remedy in comparison to antacids.

The most common reason cited by our PPI users for not taking an OTC stomach remedy to treat breakthrough symptoms was the fear of an adverse drug interaction. Although PPIs and H₂RAs can influence the metabolism and clearance of other medications by interacting with the cytochrome P₄₅₀ (CYP) 450 enzyme system, famotidine, nizatidine, and ranitidine, and the newer PPIs pantoprazole and rabeprazole, they are less likely to induce or inhibit CYP and thereby result in clinically significant drug interactions.13 Presumably physicians who are aware of significant breakthrough symptoms in their patients would recommend more effective management strategies, including concomitant H₂RA use and PPI use in selected instances.

Physicians can also reassure patients regarding the safety of appropriate use of OTC products with prescription medications and discuss possible opportunities to optimize acid-related disease management with pharmacologically sound therapeutic combinations. Furthermore, there is undoubtedly a marked underutilization of corrective lifestyle changes that can favorably affect reflux symptoms (e.g., the avoidance of bedtime snacking and tobacco use, and various dietary adjustments, including weight loss). The proper application of individualized therapy can dramatically improve symptoms in patients who suffer from gastroesophageal reflux.

It is surprising to have found such a high level of breakthrough symptoms in PPI users, a group viewed by physicians as exceptionally satisfied with their therapy. There is certainly ample justification for closely questioning patients on prescription therapy for heartburn and related symptoms; physicians can and should recommend supplementary measures to provide more complete symptom relief. Such suggestions should often include the addition of bedtime H₂RA therapy to the regimens of those PPI-takers who are experiencing significant breakthrough symptoms.

**CONCLUSION**

We conclude that breakthrough symptoms are surprisingly common in patients taking prescription therapy for heartburn and other upper GI-related symptoms. With our present knowledge of PPI pharmacology, particularly the likelihood that nocturnal acid breakthrough can be extremely common in PPI users, rational combination therapy, including concomitant H₂RA use, should be recommended to patients. Further longitudinal studies might include a direct assessment of quality of life in patients reporting breakthrough symptoms, as well as their responses to recommended adjunctive measures, including antacids, H₂RAs, and reinforcement of lifestyle modifications that might further ameliorate symptoms and reduce disease progression.

**REFERENCES**


