Gastric and Duodenal Safety of Daily Alendronate

James G. Donahue, DVM, PhD; K. Arnold Chan, MD, ScD; Susan E. Andrade, ScD; Arne Beck, PhD; Myde Boles, PhD; Diana S. M. Buist, PhD; Vincent J. Carey, PhD; Julie M. Chandler, PhD; Gary A. Chase, PhD; Bruce Ettinger, MD; Paul Fishman, PhD; Michael Goodman, PhD; Harry A. Guess, MD, PhD; Jerry H. Gurwitz, MD; Andrea Z. LaCroix, PhD; T. R. Levin, MD; Richard Platt, MD, MS

Background: Isolated case reports of gastric ulcers after alendronate sodium use raised concern about the gastroduodenal safety of daily alendronate. This study was conducted to estimate the excess risk of hospitalizations for gastric or duodenal perforations, ulcers, and bleeding associated with alendronate use.

Participants and Methods: Study subjects were 6432 men and women, 35 years or older. The subjects were members of 8 health maintenance organizations who were dispensed alendronate from October 1995 through September 1997. There was also a group of 33176 age-, sex-, and health maintenance organization–matched unexposed persons. Because of concerns that osteoporosis might confound the association between alendronate use and perforation, ulcer, or bleeding, a second comparison group of 9776 women, 60 years or older, who had osteoporotic fractures was assembled. Hospitalizations for gastroduodenal events were identified by discharge diagnosis codes in automated claims records, and confirmed by manual record review.

Results: Based on the 14 confirmed events in the alendronate group and 35 in the unexposed group, the crude incidence rate ratio of gastroduodenal perforation, ulcer, or bleeding for the alendronate cohort was 3.0. The incidence rate ratio was 1.8 (95% confidence interval, 0.8-3.9) after control for prior hospitalizations, comorbidity, and recent exposure to prescription nonsteroidal anti-inflammatory drugs and oral corticosteroids. The crude incidence ratio rate for the age, sex, and health maintenance organizations–restricted cohort of alendronate users relative to the fracture cohort was 1.1 and the adjusted incidence rate ratio was 1.1 (95% confidence interval, 0.6-2.2).

Conclusions: Osteoporosis and related factors appear to play an important role in the relationship between alendronate use and confirmed gastroduodenal perforation, ulcer, or bleeding; a substantial fraction of the increased risk we observed for alendronate users in the unadjusted analysis was the result of confounding.

Arch Intern Med. 2002;162:936-942

Ten million to 20 million postmenopausal women in the United States have osteoporosis. The enormous medical, social, and economic consequences are due primarily to osteoporotic fractures; in 1995 they were responsible for at least 400 000 hospitalizations, 2.5 million physician visits, and medical expenditures of nearly $14 billion. Several clinical trials have demonstrated the efficacy of alendronate sodium to treat osteoporosis and prevent osteoporotic fractures. Although esophageal irritation was recognized as a potential side effect of alendronate, reports to the Food and Drug Administration in 1996 and 1997 raised concern that alendronate may have previously unappreciated potential for gastric and duodenal injury, especially among the elderly.

This observational study was designed to compare the incidence of hospitalizations for gastric or duodenal perforations, ulcers, and bleeding among users of alendronate with that among a randomly selected, unexposed group. However, osteoporosis (the condition for which alendronate is indicated) is associated with excess nontrauma mortality and was therefore a potential confounder in the association between alendronate use and gastrointestinal injury. Although the prevalence of osteoporosis among the study population could not be directly measured, we sought to approximate the magnitude of this potential confounding effect by comparing the rates of gastroduodenal perforations, ulcers, and bleeding in a cohort of older women who had nonpathologic fractures with age-matched women exposed to alendronate.

RESULTS

STUDY COHORTS

A total of 6549 eligible men and women 35 years and older had 1 or more dispens-
PARTICIPANTS AND METHODS

STUDY POPULATION

This was a retrospective cohort study of health plan members of 8 health maintenance organizations (HMOs) in geographically diverse locations. The institutional review board of each HMO approved the study protocol. Membership, demographic, drug dispensing, and hospital discharge information were obtained from automated databases at each HMO. Eligible subjects were continuously enrolled in the HMO for at least 1 year after October 1, 1994 (1 year before the initial marketing of alendronate), had prescription drug coverage during the entire observation period, and had hospital records generally accessible to study personnel. Three study cohorts (alendronate, unexposed, and fracture) were identified.

The exposed cohort consisted of persons who were dispensed 10-mg tablets of alendronate at least once from October 1995 through September 1997 and were 35 years or older at the time of the first alendronate dispensing. Person-time at risk for an individual started on the date alendronate was dispensed and extended for a number of days equal to the number of tablets dispensed, according to the recommended dose of 1 10-mg tablet per day. When dispensings overlapped, the number of tablets dispensed in all such dispensings was summed and time at risk was computed from the first dispensing date. Only the first 15 days of a gap in dispensing were considered alendronate-exposed time. Person-time at risk ended on whichever of the following occurred first: September 30, 1997; first hospitalization for confirmed esophageal, gastric, or duodenal perforations, ulcers, or bleeding; disenrollment; or the date that the last dispensed alendronate pills were supposed to be taken, plus 15 days. Since the 40- and 5-mg tablets were infrequently dispensed (52 and 65 persons, respectively), individuals who were given these dosages were not included in the study.

The unexposed cohort was frequency matched to the alendronate cohort with respect to age and sex at a ratio of 5:1 within each HMO. These individuals were not given alendronate and person-time at risk for each was counted from a randomly chosen referent date after October 1, 1995, to whichever the following occurred first: September 30, 1997; first hospitalization for confirmed esophageal, gastric, or duodenal perforations, ulcers, or bleeding; or disenrollment.

The fracture cohort was composed of women older than 60 years as of October 1, 1994, judged to have a high prevalence of osteoporosis. They were from 7 of the 8 participating HMOs, and had at least 1 diagnosis code between October 1994 and September 1997 for fracture of the hip, humerus, distal tibia, vertebral, or wrist in ambulatory or hospital records. Women who had at least 1 diagnosis code that represented bone cancer, breast cancer, colon cancer, lung cancer, cancer metastasis, multiple myeloma, concurrent major trauma, or pathologic fracture were excluded. As part of a secondary analysis, the fracture cohort was further subdivided into a hip fracture group and a nonhip fracture group. Women who had multiple fractures, one being a hip fracture, were classified as having hip fracture. Diagnosis codes for hip fracture have been reported to have high predictive value positive rates. We reviewed medical records of a random sample of 404 women who fulfilled the selection criteria for nonhip fractures to evaluate the accuracy of the fracture identification algorithm. We calculated the proportion of true positives for each nonhip anatomic site at each HMO and excluded cases of fracture sites from HMOs that had a true-positive rate of less than 60%. Among the remaining fracture groups reviewed, 314 (82%) of 383 women were confirmed to have a nonpathologic fracture. Fracture-exposed person-time started on October 1, 1995, and continued until the earliest of September 30, 1997; disenrollment; first dispensing of alendronate; or first hospitalization for confirmed esophageal, gastric, or duodenal perforations, ulcers, or bleeding.

Continued on next page
Persons with upper gastrointestinal events of interest were identified in each HMO by a 3-step procedure: (1) computerized search of claims files; (2) abstraction of hospital records; and (3) confirmation of perforations, ulcers, or bleeding. Hospital claims files were searched with International Classification of Diseases, Ninth Revision, Clinical Modification codes from October 1995 through September 1997 for the discharge diagnoses of gastric ulcer (531.xx), duodenal ulcer (532.xx), peptic ulcer (533.xx), gastrojejunal ulcer (534.xx), gastrointestinal hemorrhage (578.xx), or esophageal ulcer (530.2). Full-text hospital records from hospitalizations with any one of these codes were reviewed to abstract additional information to confirm or reject the diagnosis and to determine the time of onset of signs and symptoms (before or after admission to the hospital). Three investigators (J.G.D., K.A.C., and R.P.) who were blinded to alendronate exposure status, reviewed the anonymized abstraction forms. The second reviews were conducted for all individuals except those for whom the primary review clearly indicated that there was no perforation, ulcer, or bleeding. Final arbitration of the small number of indeterminate records that remained was performed in a blinded manner by a gastroenterologist (T.R.L.).

Persons were classified as cases if they were hospitalized for esophageal, gastric, or duodenal ulcer as confirmed by surgery, endoscopy, radiology, or autopsy. In addition, cases included persons with upper gastrointestinal hemorrhage determined by surgery, endoscopy, radiology, or autopsy to originate from esophageal, gastric, or duodenal ulcer; hemorrhagic gastritis; or duodenitis. Excluded from both the case and comparison groups were persons with nonprimary esophageal ulcers concurrent with gastric or duodenal ulcers as noted above. Cases of duodenal and pyloric ulcer were classified as “duodenal ulcer.” Cases of gastric, gastrojejunal, and gastric or duodenal ulcer occurring simultaneously were classified as “gastric ulcer.”

Persons with nonprimary esophageal ulcers concurrent with gastric or duodenal ulcers were also classified by either gastric or duodenal ulcer as noted above.

ADJUSTMENT FOR COMORBIDITY

Comorbidity was assessed through the chronic disease score, which is based on age, sex, and dispensings of prescription drugs used to treat specific chronic diseases during the previous 12 months. The scores are directly related to and predictive of utilization of health care resources; higher scores reflect higher health care costs.

DATA ANALYSIS

We used the method of Breslow to estimate the incidence rate ratios (IRRs) and 95% confidence intervals (CIs). The protocol-defined primary analysis was to compare the incidence of gastric or duodenal perforations, ulcers, and bleeding among the alendronate cohort, the unexposed cohort, and the fracture cohort. Secondary analyses included the evaluation of event rates among the hip and nonhip fracture groups and comparisons with the age-sex-HMO–restricted alendronate cohort. The impact of potential effect modification and confounding by oral corticosteroids and prescription nonsteroidal anti-inflammatory drugs (NSAIDs) was assessed by stratification and regression modeling. Individuals with a confirmed event were classified as exposed to prescription NSAIDs if they were dispensed a prescription NSAID during the 45 days of eligible person-time before onset of the event. Persons without an event were classified as exposed if a prescription NSAID was dispensed during the 45 days preceding a randomly chosen date during eligible person-time. A similar strategy was used to classify oral corticosteroid exposure. We used Poisson regression to obtain the hazard rate estimates under a censored exponential event-time model.

Confidence intervals were formed with model-robust SEs that are consistent regardless of the adequacy of the exponential model for the process under consideration.
ent from the rate during alendronate-exposed time (2.4 vs 3.4 per 1000 person-years; \( P = .25 \)), but it was greater than the rate among the unexposed cohort (1.1 per 1000 person-years; \( P / H11021 \).001).

**Table 1. Baseline Characteristics of the Study Cohorts**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alendronate (Full) (n = 6432)</th>
<th>Unexposed (n = 33 176)</th>
<th>Alendronate (Women Aged ( \geq 60 ) y) (n = 3865)</th>
<th>Fracture (n = 9776)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>67 (35-97)</td>
<td>67 (35-105)</td>
<td>72 (60-97)</td>
<td>75 (60-104)</td>
</tr>
<tr>
<td>Women, %</td>
<td>92</td>
<td>91</td>
<td>100</td>
<td>100.00</td>
</tr>
<tr>
<td>Chronic disease score, median</td>
<td>3829</td>
<td>2756</td>
<td>5573</td>
<td>5495</td>
</tr>
<tr>
<td>Hospitalized during year prior to index date, %*</td>
<td>19</td>
<td>11</td>
<td>19</td>
<td>19.00</td>
</tr>
<tr>
<td>Chronic disease score categories†</td>
<td>Rheumatoid arthritis</td>
<td>26.3</td>
<td>8.9</td>
<td>30.1</td>
</tr>
<tr>
<td>Gastric acid disorder</td>
<td>24.2</td>
<td>16.0</td>
<td>37.0</td>
<td>29.2</td>
</tr>
<tr>
<td>Malignancies</td>
<td>9.8</td>
<td>2.9</td>
<td>11.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Asthma/respiratory illness</td>
<td>28.6</td>
<td>19.5</td>
<td>41.7</td>
<td>39.2</td>
</tr>
</tbody>
</table>

*Index date was date of first alendronate sodium dispensing for the alendronate cohort, the randomly selected reference date for the comparison cohort, and October 1, 1995, for the fracture cohort. Only nonfracture hospitalizations were counted for the fracture group.
†Percentage of persons with 1 or more dispensings of drugs used to treat selected chronic diseases during the year before the index date. The chronic disease score categories shown are the most directly relevant to upper gastrointestinal tract disease.

**Table 2. Rate of Confirmed Gastroduodenal Perforation, Ulcers, and Bleeding by Duration of Alendronate Therapy**

<table>
<thead>
<tr>
<th>Duration of Alendronate Therapy, d</th>
<th>1-30</th>
<th>31-90</th>
<th>( \geq 91 )</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of confirmed events*</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Person-time at risk, y</td>
<td>515</td>
<td>868</td>
<td>2755</td>
<td>4138</td>
</tr>
<tr>
<td>Incidence rate (85% CI)†</td>
<td>3.9  (0.8-14.0)</td>
<td>1.1 (0.9-6.4)</td>
<td>4.0 (2.0-7.1)</td>
<td>3.4 (1.8-5.7)</td>
</tr>
</tbody>
</table>

*Restricted to gastroduodenal events that occurred during alendronate sodium–exposed time.
†Unadjusted incidence rate (per 1000 years). \( \chi^2 \) Test for trend = 0.29, \( P = .59 \). CI indicates confidence interval.

**Table 3. Adjusted Incidence Rate Ratios for Gastroduodenal Perforation, Ulcers, and Bleeding Derived From Poisson Regression Models**

<table>
<thead>
<tr>
<th>Incidence Rate Ratio (95% CI)</th>
<th>Alendronate Users (n = 6432) vs Unexposed Cohort (n = 33 176)</th>
<th>Age-Sex-HMO–Restricted Alendronate Users (n = 3865) vs Fracture Cohort (n = 9776)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate sodium</td>
<td>1.81 (0.83-3.94)</td>
<td>1.11 (0.56-2.19)</td>
</tr>
<tr>
<td>Female</td>
<td>0.39 (0.19-0.81)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Hospitalizations during previous year†</td>
<td>1.11 (0.88-1.40)</td>
<td>1.14 (0.88-1.47)</td>
</tr>
<tr>
<td>Chronic disease score (per 1000)</td>
<td>1.06 (1.02-1.11)</td>
<td>1.06 (1.04-1.08)</td>
</tr>
<tr>
<td>Corticosteroid exposure‡</td>
<td>4.50 (1.92-10.55)</td>
<td>1.33 (0.52-3.39)</td>
</tr>
<tr>
<td>Prescription NSAID exposure‡</td>
<td>3.28 (1.70-6.33)</td>
<td>3.33 (1.94-5.72)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; HMO, health maintenance organization; and NSAID, nonsteroidal anti-inflammatory drug. Age was controlled for as indicator variables in 10-year age groups.
†Only nonfracture hospitalizations were counted for the age-sex-HMO–restricted alendronate users and the fracture cohort.
‡Exposure to corticosteroids and prescription NSAIDs was defined as a dispensing within 45 days before the date for a confirmed gastroduodenal event and within 45 days before a random date for subjects without confirmed gastroduodenal event.

Alendronate Users vs Fracture Cohort

Ten of the 14 gastroduodenal perforations, ulcers, or bleeding events among alendronate users described above were among the 3863 women of the age-sex-HMO–restricted cohort. There were 38 confirmed gastroduodenal perforations, ulcers, or bleeding events in the fracture cohort. Crude IRR for age-sex-HMO–restricted alendronate users relative to the fracture cohort was 1.1 (95% CI, 0.6-2.3). The IRR was unchanged after controlling for age, chronic disease score, recent exposure to prescription NSAIDs and oral corticosteroids, and the number of nonfracture related hospitalizations during the previous year (IRR, 1.1; 95% CI, 0.6-2.2; Table 3). Interaction terms between alendronate use and NSAID exposure and alendronate use and oral corticosteroid exposure were not significant.

When the fracture cohort was further stratified into the hip fracture group and the nonhip fracture group, the adjusted IRR of gastroduodenal perforations, ulcers, and bleeding for alendronate users relative to the hip fracture group (IRR, 0.6; 95% CI, 0.3-1.2) was substantially differ-
The ideal group with which to compare alendronate-exposed persons would have osteoporosis at the same rate and intensity but without exposure to alendronate. However, coded diagnoses of osteoporosis were not uniformly available in the automated databases of the HMOs participating in this study, and the misclassification inherent in the diagnosis of osteoporosis would result in a biased sample of persons with osteoporosis. We postulated that a comparison group consisting of older women (men were excluded from the fracture cohort) with osteoporotic fractures would be subject to less misclassification, and although not representative of all persons with osteoporosis, they would be more likely to have osteoporosis than a randomly selected comparison group. In fact, the general risk profile of the fracture cohort closely approximated the profile of the corresponding alendronate cohort; the 2 groups had comparable chronic disease scores and nonfracture hospitalization rates in the preceding 12 months. It should be noted, however, that the fracture cohort was not homogeneous with respect to the risk of gastroduodenal adverse events. Compared with women with nonhip fractures, those with hip fractures accounted for a disproportionate number of gastroduodenal perforations, ulcers, and bleeding. We do not know whether this difference is a reflection of more severe osteoporosis in women with hip fracture or whether such women have a greater prevalence of other unmeasured risk factors for these adverse events.

Although gastric and duodenal adverse events were reported in some of the alendronate clinical trials, their occurrence was no greater in those treated with alendronate than in the placebo groups.18,26 Nor were there significant differences between the treatment groups in the overall incidence of adverse events leading to discontinuation of study medication. Bauer et al26 combined the 2 study arms of the Fracture Intervention Trial and determined that the rate of gastroduodenal adverse events among over 6400 women with osteoporosis was nearly equal in the alendronate and placebo treatment groups. Although there are important methodological differences between the Bauer et al study and ours that limit comparisons (eg, their cases included hospitalized as well as nonhospitalized cases), the risks of gastroduodenal adverse events appear to be similar. For example, the event rates among alendronate-exposed women (55-64, 65-74, and 75-84 years old) in the present study were 1.1, 4.9, and 4.4 per 1000 person-years, respectively. These rates approximate the age-specific rates reported by Bauer et al.26

Nitrogen-containing bisphosphonates, including alendronate, have the potential to cause mucosal irritation. Studies in laboratory animals have demonstrated that alendronate is a topical irritant capable of inflicting erosions and enhancing indomethacin-induced ulceration of the esophagus and stomach.27,28 In addition, a number of case reports have described esophagitis and esophageal ulcers subsequent to ingestion of alendronate.9-10,29-31 Less common and conflicting have been reports of alendronate-associated gastroduodenal ulcers.11,12 A retrospective cohort study determined that older women taking alendronate were more likely to experience acid-related disorders of the upper gastrointestinal tract than a group of nonalendronate users not selected for osteoporosis.32

We conducted a retrospective cohort study of nearly 30000 persons to investigate a possible association between alendronate and confirmed gastroduodenal perforation, ulcer, or bleeding resulting in hospitalization. Because of the potential for confounding by indication (ie, osteoporosis), estimates of the effect of alendronate were computed with 2 separate comparison groups. Although neither estimate was statistically significant, they were substantially different, with a smaller (nonsignificant) excess risk when the fracture cohort was used as the comparison group. Not surprisingly, the fracture group was homogeneous with respect to the risk of these gastroduodenal events; the adjusted rate ratios were markedly different when the alendronate group was separately compared with those with hip fracture and those with nonhip fracture.

We considered osteoporosis a potential confounder of the alendronate and gastroduodenal perforations, ulcers, and bleeding relationship because of the increased morbidity and mortality in persons with osteoporosis.12-14 The excess morbidity can be attributed to underlying diseases and osteoporotic fractures, especially fractures of the hip and vertebrae33; the consequences of nonhip fractures such as wrist and humerus are substantially less.12,24 The relationship between alendronate use and upper gastrointestinal adverse events is further complicated by the increased prevalence of gastrointestinal symptoms in the elderly.25 Persons dispensed alendronate in the present study appeared to have greater morbidity than the unexposed group; they were more likely to have been hospitalized in the preceding 12 months and their chronic disease scores were higher. Moreover, they were substantially more likely to have been dispensed drugs that either predispose to peptic ulcers (eg, prescription NSAIDs and oral corticosteroids) or are used to treat conditions that may progress to peptic ulcers (eg, histamine, antagonists). Taken together, it appears that persons using alendronate may have had a greater underlying risk of a gastroduodenal adverse event than persons not using alendronate, and this may have accounted for the decrease in observed risk after control for potential confounders. Alendronate recipients’ nearly equal rate of perforation, ulcer, or bleeding during periods when they were not exposed to alendronate and periods when they were exposed lends further support to this possibility.

ESOPHAGAL PERFORATIONS, ULCERS, AND BLEEDING

There were 20 confirmed esophageal perforations, ulcers, or bleeding events without gastric or duodenal ulcers; 1 occurred during exposure to alendronate, 5 after the referent date in the unexposed group. 7 among the fracture group, and the rest occurred during ineligible person-time. No further analysis was performed for esophageal lesions because of the small number of events.
Our study had approximately 65% power to detect a 2-fold increase in risk of gastroduodenal perforations, ulcers, and bleeding for the comparison between the alendronate and the unexposed cohorts. Additional limitations pertain to the type and level of detail in automated medical records. We had no data on risk factors such as alcohol use, smoking, Helicobacter pylori infection, or family history of osteoporosis and peptic ulcer disease. Perhaps more important, we had no information on over-the-counter medications, such as nonprescription NSAIDs, that are known to promote gastrointestinal ulcers. If the alendronate-exposed individuals in our study, who were significantly more likely to have filled prescriptions for NSAIDs, were also more likely to use over-the-counter NSAIDs than those not exposed to alendronate, then we may have overestimated the relative risk of gastroduodenal perforations, ulcers, and bleeding. We probably overestimated exposure since we assumed that all dispensed alendronate tablets were taken, and we have no method to evaluate compliance using automated data. This type of misclassification of exposure would bias the effect measure toward an apparent null effect. Although the fracture types that defined the fracture cohort were known to be associated with osteoporosis, it is likely that some individuals in the fracture cohort did not have osteoporosis. Although we were not able to review all potential comorbid conditions and other factors. The role of osteoporosis as inferred from fractures is both important and complex; countervailing risks of gastroduodenal adverse events depended on the presence of hip fractures in the comparison group. A clearer understanding of the morbidity associated with osteoporosis would more completely elucidate the relationship between alendronate use and gastroduodenal perforations, ulcers, and bleeding.

Accepted for publication August 27, 2001.

From the Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital, and Harvard Medical School, Boston, Mass (Drs Donahue, Chan, Carey, and Platt); Department of Epidemiology, Harvard School of Public Health, Boston, Mass (Dr Chan); Meyers Primary Care Institute, Fallon Healthcare System, and University of Massachusetts Medical School, Worcester (Drs Andrade and Gurwitz); Kaiser Permanente Colorado, Denver (Dr Beck); Kaiser Permanente Northwest, Portland, Ore (Dr Bole); Group Health Cooperative, Seattle, Wash (Drs Buist, Fishman, and La Croix); Merck & Co, Inc, West Point, Pa (Drs Chandler and Guess); Henry Ford Health System, Detroit, Mich (Dr Chase); Kaiser Permanente Medical Care Program, Oakland, Calif (Drs Ettinger and Levin); HealthPartners Research Foundation, Minneapolis, Minn (Dr Goodman); University of California, San Francisco, School of Medicine (Dr Levin); and Department of Ambulatory Care and Prevention, Harvard Medical School, and Harvard Pilgrim Health Care, Boston, Mass (Dr Platt). Dr Ettinger received grant support from Eli Lilly, Merck & Co, Solvay, Berlex, Proctor and Gamble, and Novogen and was a paid consultant for Eli Lilly, Solvay, Berlex, Proctor and Gamble, and Durbed. Dr Levin received research support from Novartis and Merck & Co. Drs Chandler and Guess are employees and stockholders in Merck & Co.

This study was supported by a research grant from Merck & Co, Inc.

We greatly appreciate the contributions of Emily Cain, Rachel Dokholyan, and Parker Pettus. We are also grateful to Mike Allison, Charlotte Corelle, Therese DeFor, Jennifer Ellis, Barbara Mendius, Jill Mesa, Alice Pressman, Marsha Raebel, and Deborah Wood.

This study was presented, in part, as a poster at the 16th International Conference on Pharmacoepidemiology, Barcelona, Spain, August 20–23, 2000.