

SPECIAL ARTICLE

PATIENT SAFETY

Adverse Drug Events in Ambulatory Care

Tejal K. Gandhi, M.D., M.P.H., Saul N. Weingart, M.D., Ph.D., Joshua Borus, B.A., Andrew C. Seger, R.Ph., Josh Peterson, M.D., Elisabeth Burdick, M.S., Diane L. Seger, R.Ph., Kirstin Shu, B.A., Frank Federico, R.Ph., Lucian L. Leape, M.D., and David W. Bates, M.D.

ABSTRACT

BACKGROUND

Adverse events related to drugs occur frequently among inpatients, and many of these events are preventable. However, few data are available on adverse drug events among outpatients. We conducted a study to determine the rates, types, severity, and preventability of such events among outpatients and to identify preventive strategies.

METHODS

We performed a prospective cohort study, including a survey of patients and a chart review, at four adult primary care practices in Boston (two hospital-based and two community-based), involving a total of 1202 outpatients who received at least one prescription during a four-week period. Prescriptions were computerized at two of the practices and handwritten at the other two.

RESULTS

Of the 661 patients who responded to the survey (response rate, 55 percent), 162 had adverse drug events (25 percent; 95 percent confidence interval, 20 to 29 percent), with a total of 181 events (27 per 100 patients). Twenty-four of the events (13 percent) were serious, 51 (28 percent) were ameliorable, and 20 (11 percent) were preventable. Of the 51 ameliorable events, 32 (63 percent) were attributed to the physician's failure to respond to medication-related symptoms and 19 (37 percent) to the patient's failure to inform the physician of the symptoms.

The medication classes most frequently involved in adverse drug events were selective serotonin-reuptake inhibitors (10 percent), beta-blockers (9 percent), angiotensin-converting-enzyme inhibitors (8 percent), and nonsteroidal antiinflammatory agents (8 percent). On multivariate analysis, only the number of medications taken was significantly associated with adverse events.

CONCLUSIONS

Adverse events related to drugs are common in primary care, and many are preventable or ameliorable. Monitoring for and acting on symptoms are important. Improving communication between outpatients and providers may help prevent adverse events related to drugs.

From the Division of General Internal Medicine, Brigham and Women's Hospital (T.K.G., J.B., A.C.S., J.P., E.B., D.L.S., K.S., D.W.B.); the Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center (S.N.W.); the Harvard Risk Management Foundation (F.F.); and the Harvard School of Public Health (L.L.L.) — all in Boston. Address reprint requests to Dr. Gandhi at the Division of General Medicine, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at tgandhi@partners.org.

N Engl J Med 2003;348:1556-64.

Copyright © 2003 Massachusetts Medical Society.

ADVERSE DRUG-RELATED EVENTS, DEFINED as injuries due to drugs, occur frequently among inpatients.¹⁻⁴ In one study, 6.5 percent of hospitalized patients had an adverse drug event, and 28 percent of the events were preventable.⁵ Adverse drug events often lead to hospital admission. A meta-analysis⁶ estimated that in 1994 more than 1 million Americans were hospitalized because of adverse drug events, accounting for 4.7 percent of all admissions. Even though most prescribing occurs in outpatient settings, much less is known about outpatient adverse drug events than about inpatient events. Annual estimates of the proportion of outpatients with an adverse drug event range from 5 percent to 35 percent.^{7,8} In a recent retrospective study, 17 percent of outpatients reported a problem related to a prescribed medication,⁹ and in another recent study, involving Medicare enrollees living in the community, the rate of adverse drug events was 5 percent per year.¹⁰ However, few prospective data are available on the incidence of adverse drug events in the ambulatory care setting.

Several factors account for the dearth of information about adverse drug events among outpatients. Such patients obtain and administer their own medications. Since contact with physicians is intermittent, communication about problems may be infrequent. Inadequate documentation of outpatient care and high costs limit the usefulness of chart review, which is most commonly used to ascertain adverse drug events among inpatients.¹¹ These factors make it difficult to identify adverse drug events among outpatients.

We performed a study to determine the frequency, type, severity, and consequences of adverse drug events among outpatients. In addition, we assessed the preventability of such events and identified strategies to keep them from occurring or to ameliorate them.

METHODS

SITES

We studied four adult primary care practices in Boston, all of which were affiliated with academic medical centers. Two practices were hospital-based and staffed by full- and part-time teacher-clinicians, and two practices were community-based and staffed by full-time primary care physicians. One of each type of practice used a basic computerized system for prescribing drugs, and one of each type used a

manual system. The computerized systems provided printed prescriptions and information in required fields (drug, dose, quantity, and duration) but did not offer default doses in most cases and did not perform automatic checks for allergies or drug interactions. Data were collected between September 1999 and March 2000. The institutional review board approved the study. Patients were considered to have given informal consent if they completed the survey.

PHYSICIANS

All physicians at three of the sites (6 physicians at each of two sites and 5 at the third) participated in the study; 6 of 27 physicians at the fourth site were randomly selected to participate and agreed to do so. They were not blinded with respect to the purpose of the study. Once the study had begun, a seventh physician at the fourth site was added to augment the total number of patients. All physicians were board-certified internists (Table 1).

PATIENTS

Patients older than 18 years who received any prescription from participating physicians during a clinic visit (the index visit) were enrolled once during the study period (a four-week enrollment period per site). Patients were excluded if their physicians thought they were too ill or had a hearing impairment that would interfere with their participation or if they were unable to speak English or Russian. (Some of the clinics had a large number of Russian-speaking patients.)

DATA COLLECTION

One day after the index visit, we sent patients a letter describing the study as a project to improve the way in which medications are prescribed and requesting their participation in a telephone survey. Patients could decline to participate by postcard or when telephoned. Ten to 14 days after the index visit, we asked patients who agreed to participate about specific symptoms; if symptoms were present, more structured questions followed about timing and actions taken. We also asked patients to read the labels on their prescription bottles to us. Three months later, we again telephoned the patients and asked about symptoms and their general health. Also at three months, a nurse examined the medical record of each survey participant to identify any adverse drug events documented in the chart during that interval, drug allergies, and existing conditions.

Table 1. Characteristics of Physicians at the Four Clinical Practices.

Clinical Practice and Prescription System	All Physicians	Female Physicians	Mean Interval since Residency (Range)	Mean Age (Range)
	no.		yr	
Hospital-based				
Computerized	7	4	16 (7–28)	46 (33–59)
Manual	6	4	11 (4–18)	42 (33–57)
Community-based				
Computerized	5	1	10 (2–22)	39 (32–50)
Manual	6	2	12 (6–23)	41 (34–52)

ADVERSE DRUG EVENTS

Possible adverse events were reviewed independently by two of us (both physicians). The reviewers determined the likelihood that the event was related to a medication (thus meriting classification as an adverse drug event) and classified the event according to its severity and preventability. The reviewers considered the timing of symptoms, whether the patient attributed the symptoms to the drug, and the strength of published data on the relation between the symptoms and the drug. Each adverse drug event was classified as “fatal or life-threatening,” “serious,” or “significant.”¹² Events were also classified as “nonpreventable,” “preventable,” or “ameliorable.” Preventable events were those due to errors that could have been entirely avoided. Ameliorable events were those whose severity or duration could have been substantially reduced had different actions been taken. The reviewers determined preventability on the basis of the physician’s presumed knowledge at the time the drug was prescribed. If insufficient information was available, the reviewers assumed that the physician’s decision was correct. If an event was preventable or ameliorable, the reviewers specified the type of error and how it might have been prevented.

Confidence about the classification of events was rated on a six-point scale (1, little or no confidence; 2, slight-to-moderate confidence; 3, less than 50 percent confidence but a close call; 4, more than 50 percent confidence but a close call; 5, strong confidence; and 6, virtually certain). Events were excluded if the score for the confidence level was less than 4 (i.e., less than 50 percent confidence). This cutoff

point was selected a priori. Differences between the two reviewers’ judgments about the classification of events as drug-related and about the severity and preventability of such events were resolved by discussion. Interrater agreement (determined on the basis of the ratings before a consensus was reached) was high for the classification of events as drug-related (kappa, 0.89; 95 percent confidence interval, 0.79 to 0.99), their severity (kappa, 0.72; 95 percent confidence interval, 0.59 to 0.87), and their preventability (kappa, 0.70; 95 percent confidence interval, 0.62 to 0.78).

STATISTICAL ANALYSIS

We used Student’s t-test to compare continuous data; the results are presented as means \pm SE. The chi-square test was used to compare categorical data; the results are presented as counts, with percentages. All reported P values are based on two-tailed tests of significance.

The association between the characteristics of the patients and the number of adverse drug events was determined with a Poisson regression model. Only variables with a univariate association of $P < 0.25$ were introduced into the multivariate model. Clustering of variables according to the physician was accounted for with the use of a generalized estimating equation.¹³ All analyses were conducted with SAS software (SAS Institute) and Microsoft Excel.

RESULTS**RESPONSE RATES**

Of 1202 patients enrolled, 661 (55 percent) completed the survey at two weeks and of these patients, 600 (91 percent) completed the survey at three months. Chart reviews were completed for 653 of the 661 patients (99 percent). The 541 nonparticipants included 168 who refused to participate when contacted by telephone, 139 who opted out by postcard, 205 who could not be contacted, 24 who had language or hearing problems, and 5 with other reasons for not participating. The characteristics of the 661 patients who participated in the survey are shown in Table 2.

RATES OF ADVERSE DRUG EVENTS

Of the 661 patients surveyed, 162 had adverse drug events (25 percent; 95 percent confidence interval, 20 to 29 percent), with a total of 181 events (27 per 100 patients). Twenty-four of the events were se-

rious (13 percent; 95 percent confidence interval, 7 to 19 percent), 20 were preventable (11 percent; 95 percent confidence interval, 6 to 16 percent), 51 were ameliorable (28 percent; 95 percent confidence interval, 19 to 37 percent), and 11 were serious and either preventable or ameliorable (6 percent; 95 percent confidence interval, 2 to 10 percent) (Table 3). None of the events were fatal or life-threatening. The mean number of medications was significantly higher for the patients who had adverse events than for those who did not; none of the other characteristics of the patients differed significantly between the two groups (Table 2). Of the 181 adverse drug events, 166 (92 percent) were identified by surveying patients, 50 (28 percent) by reviewing charts, and 35 (19 percent) by both means. The events identified by survey and those identified by chart review did not differ significantly in terms of severity, preventability, or type of symptom; however, ameliorable events were more likely to be identified by survey than by chart review ($P=0.01$). The overall rate of adverse events did not differ significantly between clinics with computerized prescription systems and those with manual systems (25 percent and 30 percent, respectively; $P=0.29$).

TYPES OF ADVERSE DRUG EVENTS

Serious adverse drug events included symptomatic bradycardia, symptomatic hypotension, and gastrointestinal bleeding. Table 4 lists all 24 serious events, classified according to whether they were preventable or ameliorable. An example of a preventable serious event was an allergic rash in a patient for whom an antibiotic had been prescribed despite a documented allergy; an example of an ameliorable serious event was prolonged sexual dysfunction in a patient whose provider failed to discontinue a selective serotonin-reuptake inhibitor despite this symptom. Examples of significant ameliorable events include a protracted cough in a patient who continued to be treated with an angiotensin-converting-enzyme inhibitor despite the availability of alternative therapy, and prolonged sleep disturbance in a patient who was taking an antidepressant and whose physician was unaware of this symptom because the patient did not report it.

The most frequent type of adverse drug events and the most frequent preventable or ameliorable events were those related to the central nervous system (33 percent and 35 percent, respectively), gastrointestinal events (22 percent and 25 percent), and

Table 2. Characteristics of Patients According to Whether or Not They Reported Adverse Drug Events.*

Characteristic	Total (N=661)	Did Not Report Adverse Event (N=499)	Reported Adverse Event (N=162)	P Value
Age—yr				0.48
Mean	52	52	53	
Range	19–100	19–100	19–84	
Sex—no./total no. (%)				0.18
Female	433/655 (66)	321/496 (65)	112/159 (70)	
Male	222/655 (34)	175/496 (35)	47/159 (30)	
Primary language—no./total no. (%)				0.24
English	610/661 (92)	457/499 (92)	153/162 (94)	
Other	51/661 (8)	42/499 (8)	9/162 (6)	
Race or ethnic group—no./total no. (%)				0.84
White	533/654 (81)	402/496 (81)	131/158 (83)	
Black	74/654 (11)	57/496 (11)	17/158 (11)	
Other	47/654 (7)	37/496 (7)	10/158 (6)	
Educational level—no./total no. (%)				0.57
≤12 yr	113/654 (17)	83/494 (17)	30/160 (19)	
>12 yr	541/654 (83)	411/494 (83)	130/160 (81)	
Type of practice—no./total no. (%)				0.61
Hospital-based	315/661 (48)	235/499 (47)	80/162 (49)	
Community-based	346/661 (52)	264/499 (53)	82/162 (51)	
Type of prescribing—no./total no. (%)				0.29
Computerized	346/661 (52)	267/499 (54)	79/162 (49)	
Handwritten	315/661 (48)	232/499 (46)	83/162 (51)	
No. of medications				<0.001
Mean ±SE	1.53±0.04	1.42±0.04	1.85±0.09	
Range	0–6	0–5	0–6	
Duration of continuous care at clinic—no./total no. (%)				0.32
<1 yr	91/649 (14)	64/491 (13)	27/158 (17)	
1–2 yr	70/649 (11)	54/491 (11)	16/158 (10)	
2–3 yr	70/649 (11)	58/491 (12)	12/158 (8)	
>3 yr	418/649 (64)	315/491 (64)	103/158 (65)	

* Percentages may not sum to 100, because of rounding.

cardiovascular events (18 percent and 18 percent). Of the 162 patients who had an event, 26 (16 percent) reported that their symptoms required a visit to a clinical facility (19 visited an urgent care clinic, 3 went to an emergency room, and 4 went to another type of facility). Preventable or ameliorable events accounted for 9 of the 26 visits (35 percent; 6 to an urgent care clinic, 1 to an emergency room, and 2 to another type of facility).

Table 3. Rates of Adverse Drug Events.*

Variable	Adverse Events	Event Rate
	no. (%)	no./100 patients
Total adverse drug events	181	27.4
Severity		
Fatal or life-threatening	0	—
Serious	24 (13)	3.6
Significant	157 (87)	23.8
Preventability		
Ameliorable	51 (28)	7.7
Preventable	20 (11)	3.0
Not preventable	110 (61)	16.6
Serious and preventable or ameliorable	11 (6)	1.7

* Percentages may not sum to 100, because of rounding.

PREDICTORS OF ADVERSE DRUG EVENTS

None of the characteristics of the patients (age, race or ethnic group, sex, educational level, primary language, number of coexisting conditions, number of years as a patient in the practice, type of practice, or type of prescription system) were significantly associated with adverse drug events in univariate or multivariate analyses. However, the number of medications that a patient took was associated with the risk of an event ($P < 0.001$). The mean number of events per patient increased by 10 percent (95 percent confidence interval, 6 to 15 percent) for each additional medication.

MEDICATIONS ASSOCIATED WITH ADVERSE DRUG EVENTS

The medications most frequently associated with adverse drug events are shown in Table 5. Selective serotonin-reuptake inhibitors, several classes of antihypertensive agents, and nonsteroidal anti-inflammatory medications were most commonly involved. Because certain types of medications are prescribed more frequently than others, we calculated event rates on the basis of patients' reports of use (excluding drug categories with fewer than 10 patients). On this basis, the classes of medication with the highest event rates were corticosteroids, nonnarcotic analgesics, and penicillins. The highest rates of preventable or ameliorable events were associated with the use of selective serotonin-reuptake

inhibitors, calcium-channel blockers, and nonsteroidal antiinflammatory agents (Table 5).

AMELIORABLE ADVERSE DRUG EVENTS

Of the 51 ameliorable events, 32 (63 percent) were attributed to the physician's failure to respond to medication-related symptoms and 19 (37 percent) to the patient's failure to inform the physician of the symptoms. The rate of ameliorable events did not differ significantly between clinics with computerized prescription systems and those with manual systems (47 percent and 53 percent, respectively; $P = 0.87$).

PREVENTABLE ADVERSE DRUG EVENTS

Of the 20 adverse drug events that were preventable, 9 were due to the selection of an inappropriate drug, 2 to the wrong dose, and 2 to the wrong frequency of use. The rate of preventable events was the same for practices with computerized prescription systems and those with manual systems (50 percent for both, $P = 0.97$). Advanced systems of computerized medication ordering, such as those that check the dose of the drug, interactions with other drugs, and allergy to the drug, could have prevented 7 of the 20 preventable events (35 percent).

DISCUSSION

In this study of four primary care practices, we found that one quarter of outpatients had adverse drug events during a three-month period. Of these events, 13 percent were serious, 39 percent were either ameliorable or preventable, and 6 percent were serious and preventable or ameliorable. Ameliorable adverse drug events were attributed to poor communication: the physician's failure to respond to symptoms reported by the patient or the patient's failure to report symptoms to the physician. Preventable adverse drug events were due to prescribing errors, one third of which could have been prevented by the use of advanced computerized systems of prescribing medications. The characteristics of the patients were not significantly associated with adverse events, except for the number of medications taken. This finding is similar to that among inpatients¹⁴ and suggests that strategies to improve the processes of care for all patients will be more effective than strategies that target high-risk groups.

The rate of adverse drug events in our study (27 per 100 patients) was about four times as high as

Table 4. Description of Serious Adverse Drug Events.**Nonpreventable serious events (n=13)**

A middle-aged patient took a nonsteroidal antiinflammatory medication for knee pain. After three weeks of therapy, the patient was hospitalized for gastrointestinal bleeding that required transfusion and electrocautery. The medication was discontinued.

Nausea developed in an elderly patient who had recently started taking digoxin for congestive heart failure. At a subsequent office visit, the patient was found to have an elevated digoxin level (2.9 ng/ml; therapeutic range, 0.8 to 2.0), which probably caused the symptoms. The reviewers concluded that the dose of digoxin was appropriate for the patient's age and renal function.

Throat pain developed in a middle-aged patient who was taking an oral bisphosphonate. She discussed the problem with her physician, and the medication was discontinued.

An elderly patient with a history of congestive heart failure who was taking a loop diuretic had urinary incontinence that lasted more than three months. The patient discussed the symptom with the physician, and the medication was discontinued and replaced with a thiazide diuretic.

An elderly patient taking a beta-blocker had bradycardia (heart rate in the 40s). The patient was hospitalized for 24 hours, and the medication was discontinued.

An elderly patient who had been taking a beta-blocker for two weeks had shortness of breath. The medication was discontinued, and the symptom resolved.

A middle-aged patient taking a centrally acting alpha-adrenergic-receptor agonist for hypertension had bradycardia (heart rate in the 40s). The patient went to the emergency room, where an electrocardiogram was obtained, and the medication was discontinued.

A middle-aged patient taking a selective serotonin-reuptake inhibitor had sexual dysfunction of several months' duration. The patient finally told his physician, who discontinued the medication.

An elderly patient who had started taking a cyclooxygenase-2 inhibitor for pain had a severe, full-body rash that required multiple clinic visits and treatment with both an antihistamine and oral corticosteroids. The medication was discontinued.

A middle-aged patient taking a selective serotonin-reuptake inhibitor had sexual dysfunction of several months' duration. The patient finally told her physician, who discontinued the medication.

An elderly patient taking an angiotensin-converting-enzyme inhibitor for hypertension had orthostatic hypotension (systolic blood pressure in the 80s, as reported by a visiting nurse). The physician was notified and subsequently decreased the dose of the medication.

A middle-aged patient taking a selective serotonin-reuptake inhibitor was experiencing increased anxiety. The patient discussed this symptom with the physician, who discontinued the medication.

A middle-aged patient with systemic lupus erythematosus was taking a nonsteroidal antiinflammatory medication for pain (as well as oral corticosteroids and a proton-pump inhibitor). The patient had gastrointestinal distress and reported it to the physician, who discontinued the medication.

Preventable serious events (n=2)

An elderly patient with a documented allergy to a specific antibiotic received a prescription for the same antibiotic. A whole-body rash developed, and the patient was treated with epinephrine in the emergency room.

A middle-aged patient who was already taking an HMG-CoA reductase inhibitor received a prescription for an oral antifungal agent. Jaundice developed, requiring a visit to the emergency room. Use of these two medications together is contraindicated.*

Ameliorable serious events (n=9)

Three middle-aged patients who were taking selective serotonin-reuptake inhibitors had sexual dysfunction for more than three months. Although each patient discussed the symptom with the physician, no action was taken. In each case, the reviewers concluded that there are several alternative antidepressant agents that might have ameliorated the symptom.

An elderly patient taking a loop diuretic for congestive heart failure had increased urinary frequency for more than three months. The patient discussed the symptom with the physician, but no action was taken. The reviewers concluded that a dose reduction or alternate-day therapy might have ameliorated the symptom.

An elderly patient taking a beta-blocker had sexual dysfunction for more than three months. The patient discussed the symptoms with her physician, but no action was taken. The reviewers concluded that there are several alternative antihypertensive agents that might have ameliorated the symptom.

A middle-aged patient taking a selective serotonin-reuptake inhibitor had sexual dysfunction for more than three months. The patient did not discuss the symptom with her physician.

A middle-aged patient taking a selective serotonin-reuptake inhibitor and a triazolopyridine had sexual dysfunction for more than three months. The patient did not discuss the symptom with her physician.

A middle-aged patient taking a selective serotonin-reuptake inhibitor had ejaculatory dysfunction for several months. The patient eventually discussed the symptom with his physician, who substituted another selective serotonin-reuptake inhibitor. The symptom continued for another three months. The patient again discussed it with his physician, but no action was taken. The reviewers concluded that there are several alternative antidepressant agents that might have ameliorated the symptom.

A middle-aged patient taking a calcium-channel blocker for hypertension had sexual dysfunction for more than three months. The patient discussed the symptom with his physician, who prescribed sildenafil. The reviewers concluded that there are other antihypertensive agents that could have been tried before sildenafil was prescribed.

* HMG-CoA denotes 3-hydroxy-3-methylglutaryl coenzyme A.

Table 5. Medication Classes Most Frequently Associated with Adverse Drug Events.*

Medication Class	Adverse Events			Patients with Adverse Events		
	Total (N=181)	Preventable (N=20)	Ameliorable (N=51)	Any Event	Preventable Event	Ameliorable Event
	no. of events (%)			no./total no. (%) †		
Selective serotonin-reuptake inhibitors	18 (10)	0	12 (24)	18/91 (20)	0	12/91 (13)
Beta-blockers	16 (9)	2 (10)	6 (12)	16/125 (13)	2/125 (2)	6/125 (5)
Angiotensin-converting-enzyme inhibitors	15 (8)	1 (5)	7 (14)	15/131 (11)	1/131 (1)	7/131 (5)
Nonsteroidal antiinflammatory agents	15 (8)	6 (30)	1 (2)	15/93 (16)	6/93 (6)	1/93 (1)
Calcium-channel blockers	12 (7)	4 (20)	4 (8)	12/85 (14)	4/85 (5)	4/85 (5)
Penicillins	7 (4)	1 (5)	1 (2)	7/33 (21)	1/33 (3)	1/33 (3)
Oral corticosteroids	7 (4)	0	1 (2)	7/21 (33)	0	1/21 (5)
Nonnarcotic analgesic agents	6 (3)	1 (5)	0	6/19 (32)	1/19 (5)	0

* A medication class was excluded if fewer than 10 patients were taking medications in that class.

† The denominator is the total number of patients taking the medication.

that reported in studies of inpatients (about 6 per 100 admissions).^{4,5} However, these inpatient studies did not directly survey patients to identify events. In our study, patients reported three times as many events as did trained chart reviewers. The longer duration of exposure to medications among outpatients than among inpatients may contribute to the higher rate of events. The proportion of events that were serious was lower in our study (13 percent) than in one inpatient study (43 percent, including life-threatening and fatal events).⁵ However, the percentage of outpatients in our study who had serious events was actually higher than the percentage of hospitalized patients who had serious events (3.5 percent vs. 2.6 percent), because of the higher total rate of outpatient events.

In a recent study by Gurwitz et al., the frequency of adverse drug events was 5 percent per year in a population of outpatients who were 65 years of age or older.¹⁰ In that study, events were detected with a variety of approaches, including clinicians' reports, searches of computerized data for indicators of possible events, and computerized searching of electronic notes, but patients were not directly contacted. The current study includes patients who sought care and received a medication, and these patients were much younger (mean age, 52 years, vs. 75 in the study by Gurwitz et al.). The medications prescribed in this younger population also differed, with selective serotonin-reuptake inhibitors play-

ing a larger part. Even though the study by Gurwitz et al. included older patients, who would be expected to be at higher risk for adverse events because such patients take more medications, and included a year of surveillance rather than three months, the event rate in the current study was five times as high as the rate in the study by Gurwitz et al., suggesting that chart-based approaches result in a major underestimate of the true rate. Gurwitz et al. did not make the distinction between events that were preventable and those that were ameliorable, but the overall proportions of patients with preventable events were similar in the two studies. In the current study, communication issues were much more important, probably in part because such problems cannot be readily detected by chart review alone.

Most other previous studies of the frequency of adverse drug events among outpatients have been drug trials. Such studies provide valuable data because they include control groups, members of which often report many symptoms. However, these trials have limitations: the patients are generally healthier and younger than members of the general population who take medications, and patients enrolled in trials may take fewer medications overall. Studies such as ours and that of Gurwitz et al., which include a cross-section of the general population, are an important complement to clinical trials, though lack of a control group may lead to an overestimate of events.

We found that 39 percent of adverse drug events in primary care were either preventable or ameliorable. Antidepressant and antihypertensive medications were often implicated in these events, even after we accounted for the frequency with which they were prescribed. In contrast, analgesics, sedatives, and antibiotics are most commonly implicated in adverse events among inpatients.⁵ Education about these commonly prescribed medications and increased monitoring for side effects could benefit physicians and patients. In our study, most of the preventable events were due to prescribing errors (an inappropriate choice of drugs, drug interaction, or drug allergy). Computerized checks for interactions and allergies could have prevented both serious preventable events in this study, although the overall benefit of computerized prescribing in reducing adverse drug events among outpatients remains to be demonstrated.

Ameliorable adverse drug events, which were much more common than preventable events, occurred when physicians failed to respond to medication-related symptoms and when patients failed to inform physicians about such symptoms. Patients often had symptoms for months without any changes in their medications, and only a small percentage of patients reported that symptoms led to a visit to a physician. A prior study has shown that patients experience substantial anxiety and discomfort because of drug-related symptoms.⁹

Clearly, strategies to improve patient–doctor communication are essential in the outpatient setting. These strategies could include developing educational materials for patients, improving translation services, and increasing patients' access to outpatient pharmacists (to discuss medications and side effects). Some institutions have developed Web sites for patients that provide information about medications and make it possible for users to e-mail physicians.^{15,16} Such Web sites may enhance communication about medications.¹⁷ Improved strategies to monitor side effects could also be developed; for example, a nurse or pharmacist could call the patient after an office visit to inquire about any problems related to medications. Physicians' responses to symptoms could be improved by making physicians more aware of the importance of monitoring

symptoms, the prevalence and burden of adverse drug events among outpatients, and the range of therapeutic alternatives. Finally, since we identified many more events by surveying patients than by reviewing charts, strategies to improve communication should also include measures to improve documentation of adverse events in medical records.

The major limitation of our study was that it involved only four primary care practices. Although we included hospital-based and community-based practices, the results may not be generalizable. Despite the short study period, the sample was sufficiently large that our estimates of incidence are reasonably accurate. Another limitation was that we relied on patients' reports of events; however, we did confirm the reports by means of an independent review by two physicians, and there was a high level of agreement in their judgments. That these reviewers were not the patients' physicians may have been beneficial in minimizing inherent biases. In addition, response bias could have affected our surveys, although the interviewers did not specifically state that the study concerned adverse drug events. Finally, we did not ask patients why they did not inform physicians of medication-related problems, so we cannot identify underlying factors (e.g., lack of education about medications or inadequate access to physicians). Further research should focus on why patients do not report symptoms to physicians and why physicians fail to act on the reports they do receive.

Our results suggest that adverse drug events are common among outpatients, that they have important consequences, and that more than one third of such events are preventable or ameliorable. Improvements in monitoring for and responding to symptoms appear to be especially important for the prevention of adverse drug events in outpatients. In addition, improved communication between outpatients and their physicians may reduce the frequency of these events.

Supported by a grant from the Harvard Risk Management Foundation.

We are indebted to Russell Phillips, M.D., Steven Flier, M.D., Philip Triffleti, M.D., Michael Benari, M.D., Karen Victor, M.D., and Ken Farbstein, M.P.P., for their help with this project; and to Erin Hartman, M.S., for her review of the manuscript.

REFERENCES

1. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients: excess length of stay, extra costs, and attributable mortality. *JAMA* 1997;277:301-6.
2. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients: results from the Harvard Medical Practice Study II. *N Engl J Med* 1991;324:377-84.
3. Bates DW, Spell N, Cullen DJ, et al. The cost of adverse drug events in hospitalized patients. *JAMA* 1997;277:307-11.
4. Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. *JAMA* 1995;274:35-43.
5. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. *JAMA* 1995;274:29-34.
6. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;279:1200-5.
7. Hutchinson TA, Flegel KM, Kramer MS, Leduc DG, Kong HH. Frequency, severity and risk factors for adverse drug reactions in adult out-patients: a prospective study. *J Chronic Dis* 1986;39:533-42.
8. Hanlon JT, Schmader KE, Koronkowski MJ, et al. Adverse drug events in high risk older outpatients. *J Am Geriatr Soc* 1997;45:945-8.
9. Gandhi TK, Burstin HR, Cook EF, et al. Drug complications in outpatients. *J Gen Intern Med* 2000;15:149-54.
10. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003;289:1107-16.
11. O'Neil AC, Petersen LA, Cook EF, Bates DW, Lee TH, Brennan TA. Physician reporting compared with medical-record review to identify adverse medical events. *Ann Intern Med* 1993;119:370-6.
12. Folli HL, Poole RL, Benitz WE, Russo JC. Medication error prevention by clinical pharmacists in two children's hospitals. *Pediatrics* 1987;79:718-22.
13. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121-30.
14. Bates DW, Miller EB, Cullen DJ, et al. Patient risk factors for adverse drug events in hospitalized patients. *Arch Intern Med* 1999;159:2553-60.
15. Sands DZ, Halamka JD, Pellaton D. PatientSite: a web-based clinical communication and health education tool. In: HIMSS proceedings. Vol. 3. Session 114. Chicago: Healthcare Information and Management Systems Society, 2001.
16. Li YC, Kuo HS, Jian WS, et al. Building a generic architecture for medical information exchange among healthcare providers. *Int J Med Inf* 2001;61:241-6.
17. Borowitz SM, Wyatt JC. The origin, content, and workload of e-mail consultations. *JAMA* 1998;280:1321-4.

Copyright © 2003 Massachusetts Medical Society.