Incidence and Preventability of Adverse Drug Events Among Older Persons in the Ambulatory Setting

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Context Adverse drug events, especially those that may be preventable, are among the most serious concerns about medication use in older persons cared for in the ambulatory clinical setting.

Objective To assess the incidence and preventability of adverse drug events among older persons in the ambulatory clinical setting.

Design, Setting, and Patients Cohort study of all Medicare enrollees (30 397 person-years of observation) cared for by a multispecialty group practice during a 12-month study period (July 1, 1999, through June 30, 2000), in which possible drug-related incidents occurring in the ambulatory clinical setting were detected using multiple methods, including reports from health care providers; review of hospital discharge summaries; review of emergency department notes; computer-generated signals; automated free-text review of electronic clinic notes; and review of administrative incident reports concerning medication errors.

Main Outcome Measures Number of adverse drug events, severity of the events (classified as significant, serious, life-threatening, or fatal), and whether the events were preventable.

Results There were 1523 identified adverse drug events, of which 27.6% (421) were considered preventable. The overall rate of adverse drug events was 50.1 per 1000 person-years, with a rate of 13.8 preventable adverse drug events per 1000 person-years. Of the adverse drug events, 578 (38.0%) were categorized as serious, life-threatening, or fatal; 244 (42.2%) of these more severe events were deemed preventable compared with 177 (18.7%) of the 945 significant adverse drug events. Errors associated with preventable adverse drug events occurred most often at the stages of prescribing (n=246, 58.4%) and monitoring (n=256, 60.8%), and errors involving patient adherence (n=89, 21.1%) also were common. Cardiovascular medications (24.5%), followed by diuretics (22.1%), nonopioid analgesics (15.4%), hypoglycemics (10.9%), and anticoagulants (10.2%) were the most common medication categories associated with preventable adverse drug events. Electrolyte/renal (26.6%), gastrointestinal tract (21.1%), hemorrhagic (15.9%), metabolic/endocrine (13.8%), and neuropsychiatric (8.6%) events were the most common types of preventable adverse drug events.

Conclusions Adverse drug events are common and often preventable among older persons in the ambulatory clinical setting. More serious adverse drug events are more likely to be preventable. Prevention strategies should target the prescribing and monitoring stages of pharmaceutical care. Interventions focused on improving patient adherence with prescribed regimens and monitoring of prescribed medications also may be beneficial.

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Although numerous studies have evaluated the patterns and quality of prescription medication use among the elderly,[1-5] information related to the incidence of preventable adverse drug events in the ambulatory geriatric population is limited. Even though most medication errors do not result in injury,[6,7] the extensive use of medications by the geriatric population suggests that sizeable numbers of older persons are affected. The prevalence of prescription medication use among the ambulatory adult population increases with advancing age. A recent national survey of the US noninstitutionalized adult population indicated that more than 90% of persons aged 65 years or older used at least 1 medication per week.[8] More than 40% used 5 or more different medications per week, and

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12% used 10 or more different medications per week.

During recent years, the knowledge base relating to adverse drug events in hospitals and in nursing home settings has grown substantially.[9-12] However, only limited efforts have been made to systematically examine the problem of drug-related injury among the older population in the ambulatory setting. Therefore, we conducted a study of a large population of Medicare enrollees cared for in the ambulatory setting to evaluate the incidence and preventability of adverse drug events among ambulatory geriatric patients; to categorize adverse drug events by drug class, severity, and clinical effects; and to classify preventable events by the stage of the pharmaceutical care process at which the error occurred. We expect this research to inform the development and testing of interventions designed to reduce the risk of adverse drug events experienced by older persons who are receiving care in the outpatient setting.

METHODS

Study Setting and Population

This study was conducted in the setting of a large multispecialty group practice that provides care to members of a New England–based health maintenance organization. The group practice provides health care to more than 30 000 persons aged 65 years or older, approximately 90% of whom are enrolled in a Medicare + Choice Plan (Medicare risk contract with the health plan), with the remainder being traditional fee-for-service Medicare enrollees. All Medicare + Choice Plan enrollees had a drug benefit plan during the study. Traditional fee-for-service Medicare enrollees did not have a drug benefit plan under Medicare, but they may have independently purchased plans.

Box 1. Computer-Generated Signals of Possible Drug-Related Incidents

Serum Drug Levels

Quinidine >5 µg/mL
Valproate >120 µg/mL
Theophylline >20 µg/mL
Procainamide >12 µg/mL
Phenobarbital >10.4 mg/L (>45 µg/mL)
Phenytoin >20 µg/mL
Cyclosporine >400 ng/L
Digoxin >2.0 ng/mL (>2.56 nmol/L)
Carbamazepine >13.0 µg/mL

Diagnoses (*ICD-9-CM* Codes)

Poisoning by
- Psychotropic agents (969)
- Analgesics and antipyretics (965)
- Agents that affect blood (964)
- Antibiotics (960)
- Other anti-infectives (961)
- Hormones and synthetic substitutes (962)
- Anticonvulsants/antiparkinsonian drugs (966)
- Sedatives and hypnotics (967)
- Other central nervous system depressants (968)
- Central nervous system stimulants (970)
- Drugs primarily affecting the autonomic nervous system (971)
- Cardiovascular drugs (972)
- Gastrointestinal tract drugs (973)
- Water, mineral, and uric acid metabolism drugs (974)
- Agents acting on muscles and respiratory tract systems (975)
- Topical agents (976)
- Other and unspecified drugs (977)

Late effects of drugs (909)
Dermatitis due to substances taken internally (693)
Allergic contact dermatitis (692)
Neuropathy due to drugs (357.6)
Urticaria (708)
Gastritis (535.4)

Laboratory Results (Including Drug-Laboratory Combinations)

Serum alkaline phosphatase >350 U/L
Serum bilirubin >4.0 mg/dL (>68.4 µmol/L)
Serum potassium <2.9 or >6.0 mEq/L
Blood eosinophils >9%
Serum aspartate aminotransferase >84 U/L
Serum alanine aminotransferase >80 U/L
Serum urea nitrogen >60 mg/dL (>21.42 mmol/L)
International normalized ratio >5
Platelet count $<50 \times 10^3/\mu L$
Serum creatinine >2.5 mg/dL (221 µmol/L)
Thyroxine and TSH <0.3 µU/mL
Clozapine and white blood cell count $<3 \times 10^3/\mu L$
Clostridium difficile testing
Glucocorticoid and hemoglobin A_{1c} >6%
Ganciclovir and white blood cell count $<3 \times 10^3/\mu L$

Antidotes/Treatments

Prednisone and diphenhydramine
Phytonadione (vitamin K)
Naloxone
Sodium polystyrene sulfonate
Protamine sulfate
Digoxin immune antigen-binding fragments
Flumazenil
Glucagon
Hydroxyzine and prednisone
Oral vancomycin
Nystatin

Abbreviations: *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; TSH, thyroid-stimulating hormone.

Subjects for this study included all persons aged 65 years or older receiving health care services delivered by the group practice in the ambulatory setting from July 1, 1999, through June 30, 2000. Residents of long-term care facilities were excluded from the study.

The project was approved by the institutional review board of the University of Massachusetts Medical School, Worcester, and the institutional review board of the group practice and the health maintenance organization. The study was carried out under the auspices of the health plan and medical group quality management committees, as part of peer review and quality improvement activities. Study personnel had no direct contact with either patients or health care providers (which include physicians, advanced practitioners, nurses, and pharmacists) during the study.

Case-Finding Definitions and Classification of Events

Our study was limited to drug-related incidents occurring in the ambulatory clinical setting. Drug-related incidents were detected using the following methods: (1) reports from health care providers (via an intranet reporting system, adverse drug event telephone hot line, or reporting cards sent by mail); (2) review of hospital discharge summaries; (3) review of emergency department notes; (4) computer-generated signals; (5) automated free-text review of electronic clinic notes; and (6) review of administrative incident reports concerning medication errors. Ambulatory medical records were selected for review based on information derived from the various detection methods listed above. Medical record reviews and abstractions were performed by trained clinical pharmacist investigators (K.D., A.C.S., Ms Auger, and Ms Garber).

All available discharge summaries relating to hospitalizations for the study population during the study were obtained for review. The information contained in these discharge summaries was reviewed for evidence of a drug-related incident that led to an admission to the hospital. Drug-related incidents occurring during the course of a hospitalization were not considered in the context of this study. Similarly, all available emergency department notes were reviewed for evidence of a drug-related incident leading to an emergency department visit, but drug-related incidents that occurred during emergency department visits were excluded. Reviews of the discharge summaries and emergency department notes were performed by the trained clinical pharmacist investigators.

Computer-generated signals of possible drug-related incidents were derived from automated data. Such signals included elevated drug levels, abnormal laboratory results, the use of medications considered to be antidotes, and diagnoses (*International Classification of Diseases, Ninth Revision [ICD-9]*)[13] associated with health care claims that could reflect an adverse drug event. A complete list of these computer-generated signals is provided in Box 1.

Most outpatient clinic notes (>80%) were available in electronic form as part of an electronic medical record. Free-text searching, using a computer program to identify potential drug-related incidents, was conducted, as previously described by Honigman et al.[14,15] This effort involved the examination of clinic notes electronically using an adaptation of the Micromedex M^2D_2 medical data dictionary.[14,15] This data-mining tool is a clinical lexicon server consisting of a controlled vocabulary of medical concepts and drug terminology that allows for multiple relationships between multiple medical terms and events. A program was developed that semantically linked drugs and drug classes to known and reported adverse effects and their synonyms. To limit the number of false positives, links that were pursued as possible drug-related incidents by the clinical pharmacist investigators at least 15% of the time (this rate was arbitrary), during a 2-month trial period, were used in this study. Examples of drug-adverse effect links are included in Box 2.

Box 2. Examples of Drug–Adverse Effect Links

ACE inhibitors and cough
Antibiotics and diarrhea
β-Blockers and bradycardia
Calcium channel blockers and peripheral edema
Digoxin and nausea
Diuretics and hyponatremia
Diuretics and hypotension
Hypoglycemics and hypoglycemia
Hypoglycemics and tremor
NSAIDs and bleeding
NSAIDs and gastrointestinal tract complaints
NSAIDs and nausea
NSAIDs and renal insufficiency/failure
Opioids and constipation
Proton pump inhibitors and diarrhea
Selected antidepressants and anorexia
Selected antidepressants and constipation
Selected antidepressants and dry mouth
Selected antidepressants and hypotension
Selected antidepressants and insomnia
Selected antidepressants and nervousness
Warfarin and bleeding

Abbreviations: ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

Outcome Measures

The primary outcome of the study was an *adverse drug event*, defined as an injury resulting from the use of a drug. This definition is consistent with definitions used in previous studies.[9,10,12,16] Adverse drug events may have resulted from medication errors (ie, errors in prescribing, dispensing, patient adherence, and monitoring) or from adverse drug reactions in which there was no error.

After an extensive training period, we assessed reliability between clinical pharmacist investigators on the decision to select possible drug-related incidents for

Table 1. Characteristics of Medicare+ Choice Plan Enrollees

Characteristics	Enrollees, No. (%) (N = 27 617)
Age, mean (SD), y	74.7 (6.7)
Age group, y	
65-69	7110 (25.7)
70-74	7748 (28.1)
75-79	6296 (22.8)
80-84	3920 (14.2)
85-89	1871 (6.8)
≥90	672 (2.4)
Sex	
Male	11 411 (41.3)
Female	16 206 (58.7)
Length of time enrolled in health plan, mean (SD), d	351 (51)
No. of outpatient physician visits, mean (SD)	5.2 (5.2)
Outpatient physician visits	
0	3442 (12.5)
1-2	5963 (21.6)
3-4	5845 (21.2)
5-6	4206 (15.2)
>6	8161 (29.6)
No. of prescription drug dispensings, mean (SD)	21.1 (20.6)
Prescription drug dispensings	
0	3361 (12.2)
1-5	3489 (12.6)
6-15	6617 (24.0)
16-30	7273 (26.3)
>30	6877 (24.9)
No. of prescription medication categories, mean (SD)	3.8 (2.7)
Prescription medication categories	
0	3361 (12.1)
1	2689 (9.7)
2	3876 (14.0)
3	4073 (14.8)
4	3707 (13.4)
>4	9911 (35.9)

full ambulatory medical record review and abstraction. For 80 signals of possible drug-related incidents, clinical pharmacist investigators agreed 84% of the time ($\kappa = 0.67$). Four clinical pharmacist investigators were involved during the study. The agreement percentage and κ relate to pairs of clinical pharmacist investigators.

All possible drug-related incidents were presented by a clinical pharmacist investigator to pairs of physician-reviewers selected from among 4 of the authors (J.H.G., D.W.B., L.R.H., and J.R.). These physician-reviewers independently classified incidents using structured implicit review according to the following criteria: whether an adverse drug event was present, the severity of the event, whether the event was preventable, and the effects of the event on the patient. In determining whether an adverse drug event had occurred, the physician-reviewers considered the temporal relation between the drug exposure and the event, as well as whether the event reflected a known effect of the drug. The structured implicit review process has been used in numerous prior studies relating to adverse drug events across various clinical settings.[9,12,16-19]

Severity of adverse events was categorized as significant, serious, life-threatening, or fatal.[9,12] Examples of significant events include a nonurticarial skin rash, a fall without associated fracture, hemorrhage not requiring transfusion or hospitalization, and oversedation. Examples of serious events include urticaria, a fall with an associated fracture, hemorrhage requiring transfusion or hospitalization but without hypotension, and delirium. Examples of life-threatening events include hemorrhage with associated hypotension, hypoglycemic encephalopathy, profound hyponatremia, and acute renal failure requiring hospitalization. Adverse drug events were considered to be preventable if they were due to an error and were preventable by any means available.[9] Preventability was categorized as preventable, probably preventable, probably not preventable, or definitely not preventable; results were collapsed into preventable and nonpreventable categories in the analyses.[9] The effects of adverse drug events on the patients were categorized as abnormal laboratory results without signs and symptoms, symptoms of less than 1 day in duration, symptoms of 1 day and longer in duration, nonpermanent disability, permanent disability, and death. Physician-reviewers characterized an event as causing permanent disability based on the potential for a drug-induced injury with permanent effects to cause physical disability or deficits in functioning.[20]

We also classified the stages of pharmaceutical care during which an error leading to a preventable adverse drug event had occurred. The stages of pharmaceutical care in the ambulatory clinical setting were classified as prescribing, dispensing, patient adherence (eg, adherence to documented dosing or monitoring instructions provided by health care professionals), and monitoring. Monitoring stage errors include inadequate laboratory monitoring of drug therapies or a delayed response or failure to respond to signs or symptoms or laboratory evidence of drug toxicity. For a single adverse drug event, it was possible to identify errors at more than 1 stage of pharmaceutical care and/or to identify more than 1 error within a single stage of care.

When the physician-reviewers disagreed on the classification of an incident regarding the presence of an adverse drug event, its severity, or its preventability, they met and reached consensus; consensus was reached in all instances where there was initial disagreement. We compared all the initial assessments of the physician-reviewers and calculated interrater reliability using the κ statistic. For judgments about the presence of an adverse drug event, the κ was 0.81; for preventability, 0.67; and for severity, 0.66. A κ score between 0.6 and 0.8 reflects "substantial" agreement and a κ score between 0.8 and 1.0 is considered "almost perfect."[21]

Statistical Analysis

During the 12-month study, we estimated that the group practice was responsible for 30 397 person-years of health care to individuals aged 65 years or older, based on the monthly census of persons cared for by the group practice during the study, including both Medicare+Choice Plan enrollees and traditional fee-for-service Medicare patients. To determine crude rates of events, the numbers of adverse drug events were divided by the total number of person-years. Ninety-five percent confidence intervals were calculated for rate estimates.[22] We did not discount person-time from the denominator in our calculation of rates for either in-hospital stays or for short stays

in skilled nursing or rehabilitation facilities. However, long-term care residents of nursing homes were excluded from the denominator. Comparisons between categorical variables were performed using the χ^2 test. $P<.05$ was considered significant. Analyses were performed using SAS, version 8.0 (SAS Institute Inc, Cary, NC).

Administrative data regarding outpatient health service utilization and prescription medication use were available for the 27617 Medicare+Choice Plan enrollees, who were followed by the group practice at any time during the study. Comparable data for traditional fee-for-service Medicare patients were not available. To provide additional context for this study relative to other patient populations and settings, we determined age and sex characteristics, mean length of enrollment in the health plan during the study, information on frequency of outpatient physician visits, and use of prescription medications for these Medicare+Choice Plan enrollees. We also compared this population with national estimates of the overall US population aged 65 years or older (at the midpoint of the study period) with regard to age and sex distribution.

RESULTS

The characteristics and specific prescription medication categories of the 27617 Medicare+Choice Plan enrollees who were followed by the group practice at any time during the study are summarized in TABLES 1 and 2. Comparing this population to the overall US population aged 65 years and older[23] demonstrated very similar age and sex characteristics; those in age groups 65 to 74 years, 75 to 84 years, and 85 years and older comprised 53.8%, 37.0%, and 9.2% of persons in our population, respectively, compared with 52.4%, 35.3%, and 12.3% of the US population in these respective age categories. Of the US population in these age groups, 58.5% were women compared with 58.7% in our population.

The clinical pharmacist investigators identified, by the various screening methods, a total of 2268 possible drug-related incidents, of which 32.8% (745) were not characterized as adverse drug events by the physician-reviewers. Of the 1523 adverse drug events, 11.0% (168) were identified from reports submitted by health care providers, 10.8% (164) through review of hospital discharge summaries, 12.1% (184) through review of emergency department notes, 28.7% (437) through computer-generated signals, 37.1% (565) through automated free-text searching of electronic clinic notes, and less than 1% (5) through administrative incident reports concerning medication errors.

The overall rate of adverse drug events was 50.1 per 1000 person-years, with a rate of 13.8 preventable adverse drug events per 1000 person-years (TABLE 3). Of the 1523 adverse drug events, 27.6% (421) were judged preventable. Of the 578 serious, life-threatening, or fatal adverse drug events, 42.2% (244) were deemed preventable, compared with 18.7% (177) of the 945 significant adverse drug events (Table 2). Overall, more severe adverse drug events were significantly more likely to be considered preventable (relative risk, 2.25; 95% confidence interval, 1.91-2.65, $P<.001$).

Most adverse drug events (>70%) resulted in symptoms of more than 1 day in duration (TABLE 4). Sixteen events resulted in permanent disability (n=5, 0.3%) or death (n=11, 0.7%). Events resulting in permanent disability included 1 stroke, 2 intracranial bleeding events, 1 hemorrhagic injury to the eye, and 1 drug-induced pulmonary injury. Deaths in this study were related to the following: 4 fatal bleeding, 1 peptic ulcer, 1 neutropenia/infection, 1 hypoglycemia, 1 drug toxicity relating to lithium, 1 drug toxicity relating to digoxin, 1 anaphylaxis, and 1 from complications of antibiotic-associated diarrhea.

The 1523 adverse drug events were associated with a wide variety of different drug classes (TABLE 5). Cardiovascular drugs were the most frequently implicated agents (26.0%), followed by antibiotics/anti-infectives (14.7%), diuretics (13.3%), nonopioid analgesics (11.8%), anticoagulants (7.9%), hypoglycemics (6.8%), steroids (5.3%), and opioids (4.9%). Psychoactive drugs were relatively in-

Table 2. Characteristics of Medicare+Choice Plan Enrollees

Specific Prescription Medication Categories	Enrollees, No. (%) (N = 27 617)
Cardiovascular	14 691 (53.2)
Antibiotics/anti-infectives	12 299 (44.5)
Diuretics	8139 (29.5)
Opioids	6055 (21.9)
Antihyperlipidemic	5983 (21.7)
Nonopioid analgesics	5477 (19.8)
Gastrointestinal tract	5237 (19.0)
Respiratory tract	4303 (15.6)
Dermatologic	4093 (14.8)
Antidepressants	3634 (13.2)
Sedatives/hypnotics	3554 (12.9)
Nutrients/supplements	3387 (12.3)
Hypoglycemics	3180 (11.5)
Steroids	2683 (9.7)
Ophthalmics	2645 (9.6)
Thyroid	2585 (9.4)
Antihistamines	2546 (9.2)
Hormones	2514 (9.1)
Anticoagulants	1935 (7.0)
Muscle relaxants	1503 (5.4)
Osteoporosis	1457 (5.3)
Antiseizure	950 (3.4)
Antigout	893 (3.2)
Antineoplastics	764 (2.8)
Antiplatelets	369 (1.3)
Antipsychotics	325 (1.2)
Antiparkinsonians	243 (0.9)
Alzheimer disease	235 (0.9)
Immunomodulators	12 (0.04)

Table 3. Rates and Severity of Adverse Drug Events

	Type of Adverse Drug Event		
	Overall (N = 1523)	Preventable (n = 421)	Nonpreventable (n = 1102)
Rate per 1000 person-years (95% CI)	50.1 (47.6-52.6)	13.8 (12.5-15.2)	36.3 (34.1-38.4)
Category of severity, No. (%)			
Fatal	11 (0.7)	5 (1.2)	6 (0.5)
Life-threatening	136 (8.9)	72 (17.1)	64 (5.8)
Serious	431 (28.3)	167 (39.7)	264 (24.0)
Significant	945 (62.0)	177 (42.0)	768 (69.7)

Abbreviation: CI, confidence interval.

Table 4. Effects of Adverse Drug Events

	Type of Adverse Drug Event, No. (%)		
	Overall (N = 1523)	Preventable (n = 421)	Nonpreventable (n = 1102)
Abnormal laboratory results without symptoms	203 (13.3)	72 (17.1)	131 (11.9)
Duration of symptoms, d			
<1	220 (14.6)	64 (15.4)	156 (14.2)
≥1	1071 (70.3)	275 (65.3)	796 (72.1)
Disability*			
Nonpermanent	13 (0.9)	3 (0.7)	10 (0.9)
Permanent	5 (0.3)	2 (0.2)	3 (0.3)
Death	11 (0.7)	5 (1.2)	6 (0.5)

*An event was characterized as causing permanent disability based on the potential for a drug-induced injury with permanent effects to cause physical disability or deficits in functioning.

Table 5. Frequency of Adverse Drug Events by Drug Class*

	Adverse Drug Events, No. (%)		
Prescription Drug Class	Overall (N = 1523)	Preventable (n = 421)	Nonpreventable (n = 1102)
Cardiovascular	396 (26.0)	103 (24.5)	293 (26.6)
Antibiotics/anti-infectives	224 (14.7)	13 (3.1)	211 (19.1)
Diuretics	203 (13.3)	93 (22.1)	110 (10.0)
Nonopioid analgesics	180 (11.8)	65 (15.4)	115 (10.4)
Anticoagulants	121 (7.9)	43 (10.2)	78 (7.1)
Hypoglycemics	103 (6.8)	46 (10.9)	57 (5.2)
Steroids	80 (5.3)	11 (2.6)	69 (6.3)
Opioids	74 (4.9)	28 (6.7)	46 (4.2)
Antidepressants	48 (3.2)	15 (3.6)	33 (3.0)
Antiseizure	35 (2.3)	19 (4.5)	16 (1.5)
Antihyperlipidemics	30 (2.0)	2 (0.5)	28 (2.5)
Antineoplastics	26 (1.7)	1 (0.2)	25 (2.3)
Gastrointestinal tract	20 (1.3)	1 (0.2)	19 (1.7)
Nutrients/supplements	20 (1.3)	5 (1.2)	15 (1.4)
Antiplatelets	18 (1.2)	7 (1.7)	11 (1.0)
Respiratory tract	12 (0.8)	4 (1.0)	8 (0.7)
Sedatives/hypnotics	9 (0.6)	6 (1.4)	3 (0.3)
Antipsychotics	8 (0.5)	4 (1.0)	4 (0.4)
Hormones	8 (0.5)	2 (0.5)	6 (0.5)
Osteoporosis	8 (0.5)	1 (0.2)	7 (0.6)
Muscle relaxants	7 (0.5)	3 (0.7)	4 (0.4)
Thyroid	7 (0.5)	4 (1.0)	3 (0.3)
Antigout	6 (0.4)	1 (0.2)	5 (0.5)
Antiparkinsonians	4 (0.3)	0	4 (0.4)
Dermatologic	2 (1.3)	0	2 (1.8)
Alzheimer disease	2 (0.1)	1 (0.2)	1 (0.1)
Antihistamines	2 (0.1)	1 (0.2)	1 (0.1)
Immunomodulators	2 (0.1)	0	2 (0.2)
Ophthalmics	2 (0.1)	1 (0.2)	1 (0.1)
Vaccines	1 (0.1)	0	1 (0.1)

*Drugs in more than 1 category were associated with some events. Frequencies in each column sum to greater than the total number of events.

frequently implicated in adverse drug events in this population: antidepressants were associated with 3.2% of events, sedatives/hypnotics with 0.6%, and antipsychotics with 0.5%. The frequencies of adverse drug events by drug class reflected the prevalence of use of prescription medications in the source population in most, but not all, cases. Cardiovascular medications were the most frequently used prescription drug class (53.2%), followed by antibiotics/anti-infectives (44.5%), diuretics (29.5%), and opioids (21.9%) (Table 1). Antidepressants and sedatives/hypnotics were used by more than 10% of the population, yet they were implicated in few of the identified adverse events (3.2% and 0.6%, respectively).

Among the 421 preventable adverse drug events, cardiovascular drugs also were the most frequently implicated (24.5%), followed by diuretics (22.1%), nonopioid analgesics (15.4%), hypoglycemics (10.9%), anticoagulants (10.2%), and opioids (6.7%) (Table 4). While antibiotics/anti-infectives were the second most common cause of adverse drug events overall, they were associated with only 3.1% of all preventable adverse drug events. Most antibiotic/anti-infective-associated adverse drug events were rashes or diarrhea caused by *Clostridium difficile*.

Gastrointestinal tract events (eg, nausea, vomiting, diarrhea, constipation, and abdominal pain) were the most common type of adverse drug event (22.1%) and the second most common preventable adverse drug event (21.1%) after electrolyte/renal events (26.6%) (TABLE 6). Also among the most frequently identified types of preventable adverse drug events were hemorrhagic (15.9%), metabolic/endocrine (13.8%), and neuropsychiatric (8.6%) events (Table 5).

Among the 421 preventable adverse drug events, 246 (58.4%) errors were identified in the prescribing stage and 256 (60.8%) in the monitoring stage of pharmaceutical care. Of note, many preventable adverse drug events also related to errors in patient adher-

ence (n=89, 21.1%). Examples of identified errors in patient adherence include taking the wrong dose, continuing to take medication despite instructions by the physician to discontinue drug therapy, refusal to take a needed medication, continuing to take a medication despite recognized adverse effects or drug interactions known to the patient, and taking another person's medication. Dispensing errors causing preventable adverse drug events were rarely identified (<2%).

Among the preventable prescribing stage errors, wrong drug/wrong therapeutic choice errors were most common among the 421 preventable adverse drug events (n=114, 27.1%), followed by wrong dose errors (n=101, 24.0%). Inadequate patient education concerning medication use was cited as an error in 18% (75) of preventable adverse drug events. The prescription of a drug for which there was a well-established, clinically important interaction with another drug (eg, drug interaction with warfarin) also was a common error (n=56, 13.3%).

Monitoring stage errors generally represented inadequate laboratory monitoring of drug therapies or a delayed response or failure to respond to signs or symptoms of drug toxicity or laboratory evidence of drug toxicity. Failure to act on available information relating to clinical findings or laboratory results was the most common error that occurred at the monitoring stage (n=154, 36.6%), followed closely by inadequate monitoring (n=152, 36.1%). Examples of monitoring errors include inadequate frequency of monitoring of warfarin leading to an elevated international normalized ratio value associated with bleeding, and failure to respond promptly to symptoms suggestive of digoxin toxicity (eg, nausea, vomiting, and anorexia).

COMMENT

We found that adverse drug events were common among ambulatory geriatric patients, and that more than a quarter were preventable. Serious, life-threatening, and fatal adverse drug events were more likely to be preventable than less severe events. The types of medications most commonly involved in adverse drug events relate closely to those most frequently prescribed in the ambulatory setting, with cardiovascular drugs and antibiotics/anti-infectives being the most frequently used and implicated drug categories. While most adverse drug events had few long-term consequences, disability and some deaths occurred.

Although it is difficult to directly compare event rates observed in the present study with studies performed in other clinical settings involving different patient populations, some comparisons are of interest. Bates et al[9] identified adverse drug events occurring during 4031 nonobstetrical adult admissions to 2 Boston tertiary care hospitals during a 6-month period. Of the 247 adverse drug events identified in that study (6.5 adverse drug events per 100 admissions), 1% were fatal, 12% were life-threatening, 30% were serious, and 57% were significant; and 28% of these were judged preventable. Of the serious and life-threatening adverse events, 42% were judged preventable compared with 18% of significant adverse drug events. Gurwitz et al[12] identified 546 adverse drug events during 2403 nursing home resident-years of observation (227 adverse drug events per 1000 resident-years) in 18 Massachusetts nursing homes. Of the adverse drug events, 1 was fatal, 6% were life-threatening, 38% were serious, and 56% were significant; and 51% of these were judged preventable. Of the serious, life-threatening, and fatal events, 72% were judged preventable compared with 34% of the significant events. In the ambulatory setting, the percentage of adverse drug events that were deemed preventable more closely mirrored the hospital setting (28%). Consistent with

Table 6. Frequency of Types of Adverse Drug Events*

Type	Adverse Drug Events, No. (%)		
	Overall (N = 1523)	Preventable (n = 421)	Nonpreventable (n = 1102)
Gastrointestinal tract	336 (22.1)	89 (21.1)	247 (22.4)
Electrolyte/renal	255 (16.7)	112 (26.6)	143 (13.0)
Hemorrhagic	194 (12.7)	67 (15.9)	127 (11.5)
Metabolic/endocrine	145 (9.5)	58 (13.8)	87 (7.9)
Dermatologic/allergic	120 (7.9)	9 (2.1)	111 (10.1)
Infection	91 (6.0)	2 (0.5)	89 (8.1)
Respiratory tract	83 (5.4)	12 (2.9)	71 (6.4)
Neuropsychiatric	75 (4.9)	36 (8.6)	39 (3.5)
Edema	72 (4.7)	6 (1.4)	66 (6.0)
Syncope/dizziness	72 (4.7)	20 (4.8)	52 (4.7)
Cardiovascular	66 (4.3)	25 (5.9)	41 (3.7)
Hepatic	23 (1.5)	3 (0.7)	20 (1.8)
Anorexia/weight loss	18 (1.2)	8 (1.9)	10 (0.9)
Ataxia/difficulty with gait	15 (1.0)	6 (1.4)	9 (0.8)
Falls without injury	15 (1.0)	10 (2.4)	5 (0.5)
Hematologic	14 (0.9)	1 (0.2)	13 (1.2)
Anticholinergic†	12 (0.8)	4 (1.0)	8 (0.7)
Fall with injury	8 (0.5)	4 (1.0)	4 (0.4)
Musculoskeletal	5 (0.3)	1 (0.2)	4 (0.4)
Extrapyramidal symptoms/tardive dyskinesia	4 (0.3)	0	4 (0.4)
Functional decline‡	3 (0.2)	1 (0.2)	2 (0.2)
Incontinence	1 (0.1)	0	1 (0.1)

*Adverse drug events could manifest as more than 1 type.
†Anticholinergic effects include dry mouth, dry eyes, urinary retention, and constipation.
‡Adverse drug event manifested only as decline in activities of daily living without any other more specific type of event. Other types of events may have been associated with functional decline.

both the hospital and nursing home settings, more serious events were more likely to be judged preventable.

Electrolyte/renal, gastrointestinal tract, hemorrhagic, and metabolic/endocrine events were the most common types of preventable adverse drug events identified in our study. Some of these types of events may be more amenable to prevention efforts than others. Technological approaches, such as computerization of prescribing with clinical decision support, have the potential to reduce the occurrence of drug-induced nephrotoxicity, dehydration, and electrolyte abnormalities.[24,25] Computerized physician order entry with decision support provides the potential to prevent or to warn against prescribing drugs with known interactions, or to warn the prescriber of a need to increase the frequency of monitoring. Active prompting of the prescriber to perform follow-up laboratory testing in the case of prescribing anticoagulants, thyroid medications, antiseizure medications, and certain cardiovascular drug therapies (eg, digoxin and angiotensin-converting enzyme inhibitors) is feasible. While there is evidence to support the benefits of this approach in the inpatient setting,[26] less than 5% of US hospitals have computerized physician order entry.[27,28] Use of such systems in the ambulatory setting is even more limited; while this approach may be equally useful in the ambulatory setting, evidence supporting the benefits remains largely anecdotal.[29]

Anticoagulants were responsible for 121 of the 1523 adverse drug events, fully a third of which were considered preventable. A more systematic approach to decision making about the use of warfarin for stroke prevention in older persons is required, as is a more consistent approach to management of anticoagulant therapy. While more widespread use of specialized clinics for anticoagulation therapy to provide coordinated care has been promoted to improve the effectiveness and safety of warfarin in elderly patients,[30] to date the benefits of this approach relative to usual care have not been established.[31]

While most antibiotic-associated events were characterized as nonpreventable, it is widely recognized that these agents are commonly overused, particularly in the ambulatory setting.[32] Many antibiotic-associated events (eg, rashes and diarrhea) might have been deemed preventable if the decision to implement therapy had been more rigidly scrutinized.

Most errors associated with preventable adverse drug events occurred at the prescribing and monitoring stages. However, problems with patient adherence were cited as a contributing factor in more than 20% of cases. The issue of patient adherence has received very little attention in the literature on patient safety relevant to preventing adverse drug events, but this issue is clearly very important.[26,33] In studies of preventable adverse drug events conducted in hospital and long-term care settings, errors involving patient adherence have not been identified as an important issue. In those clinical settings, all aspects of pharmaceutical care are presumed to be supervised; generally the patient is given little, if any, responsibility relating to medication administration or monitoring. In contrast, in the ambulatory setting, such responsibilities do extend to the patient and/or family members. While the adverse effects of patient nonadherence on the therapeutic benefits of drug therapies have been increasingly recognized,[34] the effect of nonadherence on the risk of adverse drug events has not been widely considered. As patient education is an essential component of most efforts to improve patient adherence, it is informative that our study identified inadequate patient education about medication use as a frequent error in preventable adverse drug events.

Our study was conducted in the context of a single multispecialty group practice providing care to older persons aged 65 years or older residing in a single geographic area, and the vast proportion of the study population was composed of Medicare+Choice Plan enrollees. This particular setting is ideal for such research, as automated data on prescription medications, laboratory results, and electronic clinic notes are readily available. At the time of our study, while only 17% of all Medicare beneficiaries nationally were Medicare+Choice Plan enrollees,[35] the age and sex characteristics of the study population closely mirrored the overall US population aged 65 years or older.[23]

If the findings of the present study are generalized to the population of all Medicare enrollees, then more than 1 900 000 adverse drug events—more than a quarter of which are preventable—occur each year among 38 million Medicare enrollees; furthermore, estimates based on our study suggest that there are in excess of 180 000 life-threatening or fatal adverse drug events per year, of which more than 50% may be preventable. For a number of reasons, these estimates are likely to be conservative. In our study, while most outpatient notes (>80%) were available in electronic form as part of an electronic medical record, handwritten notes were not systematically searched, which likely reduced complete ascertainment of adverse events. To ascertain information on drug-related incidents, we relied solely on information contained in ambulatory medical records. The clinical pharmacist investigators were cued to review ambulatory medical records by a variety of information sources including automated signals, hospital discharge summaries, emergency department notes, spontaneous reports by health care providers, and administrative incident reports, but they did not review every medical record. However, a systematic, periodic review of all medical records would likely have provided the opportunity to identify even more adverse drug events. In addition, in some cases, information contained in ambulatory records was limited, and adequate information was not available to allow physician-reviewers to classify incidents as adverse drug events. There was no direct patient contact in this study; interviews of patients would have provided the opportunity to identify additional events.[36]

We did not discount person-time from the denominator in our calculation of rates for time spent in hospital or for short stays in skilled nursing or rehabilitation facilities. However, we suspect that this would modestly affect our estimates, even if such adjustments were made. For example, recently published data from the National Center for Health Statistics indicate that for the year 2000 in the United States, persons aged 65 years or older had an average of 2 days of hospital care.[37]

The interrater reliability of implicit judgments about adverse events caused by medical care, based on medical record review, has been criticized.[38] However, in the present study, we found a high level of agreement between the physician-reviewers. Several authors have been highly critical of estimates of numbers of deaths caused by medical error, citing a need to be certain that the adverse event caused death in a patient who otherwise would have survived.[39-41] Our study was not designed to focus on death as a primary outcome measure. As Hayward and Hofer have written, "Whether errors warrant systems changes should not be based on the impact of the errors but, rather, on a careful examination of specific errors and the effectiveness and costs of a policy directed at error prevention."[42]

How should the findings of this study be applied to improve the quality of care for older persons in the ambulatory setting? Fortunately, many health care systems are moving toward an approach to dealing with medical error by addressing failure in the design of systems of care that contribute to error.[7,43,44] Enhanced surveillance and reporting systems for adverse drug events in the ambulatory setting are required. Efforts as intensive as those described in the present study would not be feasible on an ongoing basis because of their expense, but automated monitoring of some type may be practical as electronic medical record systems are more widely adopted. However, almost no such monitoring currently takes place in the outpatient setting.

Prescribing and monitoring errors in the ambulatory setting may be particularly amenable to prevention strategies using systems-based approaches. Broader testing of computerized physician order entry with clinical decision support to reduce the risk of medication errors is required before advocating for large-scale implementation in the outpatient setting. Further development and testing of new approaches to enhance collaborations between those who prescribe drugs and those who know the most about the specific drugs, that is, clinical pharmacists, should be pursued in the ambulatory setting.[16,45]

The increased involvement of older persons in their pharmaceutical care also has the potential to be particularly beneficial in reducing medication errors. Complex medication regimens can lead to confusion for elderly patients and family members. Physicians and pharmacists are generally relied on to provide accurate and complete drug instructions for administration and monitoring to patients and their families. However, these interactions are often hurried, leading to the provision of incomplete information.[46] As Kaushal et al[29] have advocated for use by parents of pediatric patients, World Wide Web–based information could supplement verbal information provided by physicians and pharmacists. Personalized Web pages could provide information regarding a specific medication regimen and enhance patient adherence.

In summary, adverse drug events are common and often preventable among older persons in the outpatient setting. Our study provides additional evidence of the need to develop and evaluate new strategies to reduce the risk of drug-related injury in the ambulatory geriatric patient population.

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. . . we do not know a truth without knowing its cause.
—Aristotle (384-322 BCE)