National Surveillance of Emergency Department Visits for Outpatient Adverse Drug Events

Daniel S. Budnitz, MD, MPH
Daniel A. Pollock, MD
Kelly N. Weidenbach, MPH
Aaron B. Mendelsohn, PhD, MPH
Thomas J. Schroeder, MS
Joseph L. Annest, PhD

Context Adverse drug events are common and often preventable causes of medical injuries. However, timely, nationally representative information on outpatient adverse drug events is limited.

Objective To describe the frequency and characteristics of adverse drug events that lead to emergency department visits in the United States.

Design, Setting, and Participants Active surveillance from January 1, 2004, through December 31, 2005, through the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project.

Main Outcome Measures National estimates of the numbers, population rates, and severity (measured by hospitalization) of individuals with adverse drug events treated in emergency departments.

Results Over the 2-year study period, 21 298 adverse drug event cases were reported, producing weighted annual estimates of 701 547 individuals (95% confidence interval [CI], 509 642-893 452) or 2.4 individuals per 1000 population (95% CI, 1.7-3.0) treated in emergency departments. Of these cases, 3487 individuals required hospitalization (annual estimate, 117 318 [16.7%]; 95% CI, 13.1%-20.3%). Adverse drug events accounted for 2.5% (95% CI, 2.0%-3.1%) of estimated emergency department visits for all unintentional injuries and 6.7% (95% CI, 4.7%-8.7%) of those leading to hospitalization and accounted for 0.6% of estimated emergency department visits for all causes. Individuals aged 65 years or older were more likely than younger individuals to sustain adverse drug events (annual estimate, 4.9 vs 2.0 per 1000; rate ratio [RR], 2.4; 95% CI, 1.8-3.0) and more likely to require hospitalization (annual estimate, 1.6 vs 0.23 per 1000; RR, 6.8; 95% CI, 4.3-9.2). Drugs for which regular outpatient monitoring is used to prevent acute toxicity accounted for 41.5% of estimated hospitalizations overall (1381 cases; 95% CI, 30.9%-52.1%) and 54.4% of estimated hospitalizations among individuals aged 65 years or older (829 cases; 95% CI, 45.0%-63.7%).

Conclusions Adverse drug events among outpatients that lead to emergency department visits are an important cause of morbidity in the United States, particularly among individuals aged 65 years or older. Ongoing, population-based surveillance can help monitor these events and target prevention strategies.

JAMA. 2006;296:1858-1866 www.jama.com

OUTPATIENT USE OF DRUG therapies in the United States is common and may confer serious risks along with substantial therapeutic benefits.[1,2] Historically, the public health burden of adverse events from therapeutic drug use among community-dwelling, nonhospitalized patients has been difficult to estimate, but the problem is large and can be expected to increase.[3-5] In 2004, 82% of the US population reported using at least 1 prescription medication, over-the-counter medication, or dietary supplement in the previous week and 30% reported using 5 or more of these drugs.[1]

Outpatient drug use will likely increase due to an aging population, the trend toward outpatient service delivery, the development of new prescription medications, the transition of prescription medications to over-the-counter availability, and the increasing use of drugs for chemoprevention. The recent implementation of the new Medicare prescription drug coverage benefit is designed to provide beneficiaries with additional financial support to help ensure their continued access to drug treatments,[6] which may further increase outpatient drug use.

These trends underscore the need for ongoing surveillance of outpatient drug safety. Although much attention and effort have been directed to measuring, understanding, and preventing adverse drug events (ADEs) in hospitalized patients,[7,8] less attention has been focused on ADEs occurring outside of health care facilities. This is due in part to the difficulty of obtaining timely, nationally representative surveillance data on outpatient ADEs.[9]

To enhance surveillance of outpatient drug safety, the Centers for Disease Control and Prevention (CDC), the US Consumer Product Safety Commission (CPSC), and the US Food and Drug

Author Affiliations: Division of Healthcare Quality Promotion, National Center for Infectious Diseases, Coordinating Center for Infectious Diseases (Drs Budnitz and Pollock and Ms Weidenbach), Office of Statistics and Programming, National Center for Injury Prevention and Control (Dr Annest), Centers for Disease Control and Prevention, Atlanta, Ga; Office of Drug Safety, Center for Drug Evaluation and Research, US Food and Drug Administration, Rockville, Md, and Epidemic Intelligence Service, Office of Workforce and Career Development, Centers for Disease Control and Prevention (Dr Mendelsohn); and US Consumer Product Safety Commission, Bethesda, Md (Mr Schroeder). Dr Mendelsohn is now director of epidemiology, Product Safety, MedImmune, Gaithersburg, Md.
Corresponding Author: Daniel S. Budnitz, MD, MPH, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mailstop A-24, Atlanta, GA 30333 (dbudnitz@cdc.gov).

Administration (FDA) developed the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (NEISS-CADES). We report data from the first 2 years of NEISS-CADES to estimate and describe the national burden of ADEs that led to emergency department (ED) visits.

METHODS

Setting and Population

The 63 hospitals participating in the National Electronic Injury Surveillance System–All Injury Program (NEISS-AIP) are a nationally representative, stratified probability sample of all hospitals (excluding psychiatric and penal institutions) in the United States and its territories, with a minimum of 6 beds and a 24-hour ED.[10] There are 4 size strata (very large, large, medium, and small) based on the number of annual ED visits and 1 children's hospital stratum.

The CPSC and CDC jointly train coders located at each hospital who review clinical records of every ED visit to identify all initial visits for injuries, poisonings, and ADEs. Approximately 500 000 injury-related ED visits are reported to NEISS-AIP each year. Participation by hospitals in NEISS-AIP is voluntary and confidentiality of all data is ensured by the Consumer Product Safety Act.[11] Data collection, management, quality assurance, and analyses were determined to be public health surveillance activities by CDC and FDA human subjects oversight bodies and therefore did not require human subject review or institutional review board approval.

Case Definition and Data Collection

For the Cooperative Adverse Drug Event Surveillance (CADES) component of NEISS-AIP, an adverse drug event case is defined as an incident ED visit for a condition that the treating physician explicitly attributed to the use of a drug or a drug-specific effect. Coders are instructed to examine the physician diagnoses recorded in the clinical record. If a condition is specifically linked to a drug in this section, then the case is included. If a diagnosis describes a condition commonly related to drug effects (eg, bleeding, hypoglycemia) coders examine other sections of the clinical record for evidence that the condition is, in fact, drug-related (eg, documentation of supratherapeutic international normalized ratio [INR] in a patient taking anticoagulants, documentation of insulin use in a patient with hypoglycemia).

Drugs include prescription or over-the-counter (OTC) medications; vaccines; and vitamins, dietary supplements, and herbal products. (In its organizations, operations, and regulations, the FDA distinguishes drug products from vaccines, vitamins, and dietary supplements. Drugs and vaccines require FDA approval before they can be sold; vitamins and dietary supplements do not.) Alcoholic beverages, tobacco products, and illicit substances are excluded.

Adverse events include allergic reactions (immunologically mediated effects)[12]; adverse effects (undesirable pharmacologic or idiosyncratic effects at recommended doses)[12]; unintentional overdoses (toxic effects linked to excess dose or impaired excretion)[12]; or secondary effects (eg, falls, choking). Intentional self-harm (eg, suicide attempts), drug therapeutic failures, drug withdrawal, and drug abuse are excluded. Adverse drug events that occur as a result of medical treatment received during the ED visit are excluded. Follow-up visits for an ADE previously diagnosed and treated are also excluded.

After identifying ADE cases, NEISS-AIP coders transcribe physician diagnoses and abstract from the clinical record the reason for visit, diagnostic tests, therapies administered, and the name, dose, route, frequency, and duration of use for up to 2 drugs associated with the adverse event. Coders also record up to 10 concomitant drugs as well as core NEISS-AIP data elements such as patient demographics and a narrative description of the incident. NEISS-AIP coders use a computer-based data entry system to transmit case reports to CPSC for initial quality review. Deidentified data are forwarded to CDC for further review and quality assurance. NEISS-AIP hospital coders and their supervisors receive specific instruction on identifying ADEs and abstracting additional data through training conferences, a coding handbook, electronic training materials, practice exercises, supplemental coding tools, and individual hospital reviews and site visits.[13,14]

Outcome Measures

In this study, an ED visit for an ADE was the primary outcome measure. A secondary clinical outcome was ADE severity as measured by the need for hospitalization following ED evaluation. Hospitalization includes admission to an inpatient unit of that facility, admission to the ED for observation, or transfer to another facility for acute medical care. NEISS data, including ADE data, are not used for national estimates of deaths. Details about event circumstances are often lacking when patients are dead on arrival or die soon after arrival in the ED, and such cases are incompletely captured across ED record systems. Therefore, deaths from ADEs occurring in the out-of-hospital setting, in the ED, or after hospital admission are not reported.

Data Analysis

To describe the magnitude and epidemiology of ADEs treated in EDs, we classified ADEs by patient, event, and drug characteristics. Narrative summaries, clinical testing, and physician diagnoses were coded through FDA using the Medical Dictionary for Regulatory Activities (MedDRA) version 7.0 preferred terms, an international terminology used to analyze adverse event reports.[15] Type of ADE and type of condition were categorized using the MedDRA terms describing diagnoses and symptoms.

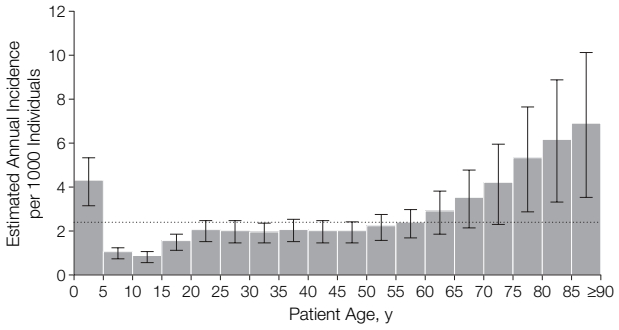
Drugs were categorized by active ingredient and route of administration using the National Drug File Reference Terminology (acquired August 2003).[16] Drugs not included in the National Drug File Reference Terminology (eg, certain nutritional supplements and OTC preparations) and drugs included in multiple classes were classified by the investigators. The following drugs were considered to commonly require regular moni-

Table 1. Number of Cases and Annual Estimate of Individuals With Unintentional Injuries and Adverse Drug Events Treated in Emergency Departments by Age and Sex—United States, 2004-2005

	Overall					Hospitalizations*				
	Unintentional Injuries†		Adverse Drug Events			Unintentional Injuries†		Adverse Drug Events		
Patient Characteristic	Cases, No.	Annual Estimate, No. (%)	Cases	Annual Estimate, No. (%)	Adverse Events, %	Cases	Annual Estimate, No. (%)	Cases	Annual Estimate, No. (%)	Adverse Events, %
Age, y‡										
0-4	104 185	2 287 674 (8.2)	3674	85 918 (12.2)	3.8	3641	64 002 (3.7)	484	9390 (8.0)	14.7
5-17	225 082	5 704 076 (20.6)	2265	53 396 (7.6)	0.9	7642	153 572 (8.8)	277	3782 (3.2)	2.5
18-44	362 044	11 839 904 (42.7)	6370	222 318 (31.7)	1.9	17 923	513 271 (29.3)	522	18 395 (15.7)	3.6
45-64	147 178	4 908 006 (17.7)	4497	162 412 (23.1)	3.3	11 864	373 570 (21.3)	783	28 417 (24.2)	7.6
≥65	83 549	3 010 917 (10.8)	4492	177 504 (25.3)	5.9	18 533	648 695 (37.0)	1421	57 336 (48.9)	8.8
Sex§										
Female	412 534	12 609 421 (45.4)	12 606	425 016 (60.6)	3.4	26 667	827 005 (47.2)	1937	67 102 (57.2)	8.1
Male	509 510	15 138 895 (54.6)	8687	276 304 (39.4)	1.8	32 975	926 320 (52.8)	1549	50 174 (42.8)	5.4
Total	922 196	27 753 656 (100.0)	21 298	701 547 (100.0)	2.5	59 664	1 754 210 (100.0)	3487	117 318 (100.0)	6.7

*Hospitalizations include patients who were admitted to an inpatient unit of the health care facility, transferred to another health care facility, or held in the emergency department as observation admissions.
†Unintentional injuries were defined as injuries or poisonings that are not inflicted by deliberate means (ie, not on purpose) and include adverse drug events.
‡Patient age was unavailable for 158 unintentional injury cases, of which 61 were hospitalized.
§Patient sex was unavailable for 152 unintentional injury cases, of which 22 were hospitalized. Patient sex was unavailable for 5 adverse drug event cases, of which 1 was hospitalized.

Figure. Estimated Annual Incidence of Adverse Drug Events Treated in US Emergency Departments



The estimated annual population rate of adverse drug events (dotted line) is 2.4 per 1000 (95% confidence interval, 1.7-3.0). Error bars represent 95% confidence intervals. Data are from the 2004-2005 National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project.

toring because of a narrow therapeutic range: insulins, oral hypoglycemic agents, warfarin, digitalis glycosides, phenytoin, carbamazepine, divalproex, primidone, lithium, and theophylline.

Statistical Analysis

Each NEISS-AIP case is assigned a sample weight based on the inverse probability of selection.[10] These weights were summed and the sum divided by 2 to determine annual national estimates of ADEs in the period 2004-2005. Population ADE rates were calculated using 2004 and 2005 US population estimates from the US Census Bureau[17,18] and were considered free of sampling error. Estimates and 95% confidence intervals (CIs) were calculated using the *surveymeans* procedure in SAS version 9.1 to account for the sample weights and complex sample design (SAS Institute Inc, Cary, NC). Estimates of less than 1200 individuals, based on fewer than 20 cases, or with coefficients of variation (CVs) greater than 30% may be unstable[19] and are indicated in the tables.

RESULTS

Based on 21 298 ADE cases reported, we estimated that 701 547 US patients (95% CI, 509 642-893 452) were treated annually for ADEs in EDs in 2004 and 2005. Of these, 3487 case patients were hospitalized (annual estimate, 117 318 [16.7%]; 95% CI, 13.1%-20.3%). The hospitalized cases included 2932 admitted to an inpatient unit of the facility (annual estimate, 13.8%; 95% CI, 10.5%-17.1%), 385 held in the ED as observation admissions (annual estimate, 1.9%; 95% CI, 0.5%-3.4%), and 170 transferred to another health care facility (annual estimate, 1.0%; 95% CI, 0.7%-1.3%).

Based on 922 196 unintentional injury and ADE cases reported to NEISS-AIP, 2.5% (95% CI, 2.0%-3.1%) of estimated ED visits were due to ADEs and 6.7% (95% CI, 4.7%-8.7%) of estimated hospitalizations for unintentional injuries were due to ADEs (TABLE 1). Patients aged 65 years or older comprised 10.8% of all estimated unintentional injury visits (95% CI, 9.6%-12.1%) but 25.3% of estimated ADE visits (95% CI, 20.2%-30.4%). Patients aged 65 years or older accounted for 37.0% of estimated unintentional injury visits requiring hospitalization (95% CI, 31.8%-42.2%) but 48.9% of estimated ADE visits requiring hospitalization (95% CI, 40.0%-57.8%). While most ED visits for unintentional injuries overall were among

men (annual estimate, 54.6%; 95% CI, 53.7%-55.5%), most ED visits for ADEs were among women (annual estimate, 60.6%; 95% CI, 59.1%-62.1%). Based on 4 451 726 total ED visits reported to NEISS (annual estimate, 120 490 979 visits), ADEs led to 0.6% of estimated ED visits for all causes.

The estimated annual population rate of ADEs treated in EDs was 2.4 per 1000 individuals (95% CI, 1.7-3.0). In infants and children younger than 5 years, the estimated annual rate of ADEs (4.3 per 1000; 95% CI, 3.1-5.4) was higher than the estimated annual rate for the general population rate but dropped among children aged 5 through 9 years (1.0 per 1000; 95% CI, 0.7-1.3) (FIGURE). The estimated annual rate of ADEs began to exceed the general population rate again in adults aged 60 through 64 years (2.9 per 1000; 95% CI, 1.9-3.9) and continued to increase with age until peaking at 6.8 per 1000 for adults aged 85 years or older (95% CI, 3.6-10.1). The estimated annual rate of ADEs for individuals aged 65 years or older was more than twice the rate for those younger than 65 years (4.9 per 1000; 95% CI, 2.7-7.0 vs 2.0 per 1000; 95% CI, 1.6-2.5) (rate ratio [RR], 2.4; 95% CI, 1.8-3.0). Overall, the estimated annual population rate of ADEs requiring subsequent hospitalization was 0.4 per 1000 (95% CI, 0.2-0.6). For persons aged 65 years or older, the estimated annual population rate of ADEs requiring hospitalization was nearly 7 times the rate for persons younger than 65 years (1.6 per 1000; 95% CI, 0.7-2.5 vs 0.23 per 1000; 95% CI, 0.15-0.31) (RR, 6.8; 95% CI, 4.3-9.2).

The most common conditions caused by ADEs were dermatologic, gastrointestinal, and neurological conditions (TABLE 2). Most adverse events manifested as a single type of condition (14 137 cases; annual estimate, 64.1%; 95% CI, 61.0%-67.4%). A quarter of adverse events involved 2 types of conditions (5353 cases; annual estimate, 26.6%; 95% CI, 25.0%-28.2%). Fewer adverse events involved 3 or more conditions (1808 cases; annual estimate, 9.3%; 95% CI, 7.0%-11.7%).

One third of estimated ED visits were attributed to allergic reactions (33.5%; 95% CI, 28.6%-38.4%), and one third were attributed to unintentional overdoses (32.1%; 95% CI, 28.6%-35.7%) (TABLE 3). Most of the estimated hospitalizations were attributed to unin-

Table 2. Number of Cases and Annual Estimate of Individuals With Adverse Drug Events Treated in Emergency Departments by Condition—United States, 2004-2005

	Adverse Drug Events	
Condition	Cases, No.	Annual Estimate, No. (%)*
Dermatologic	5323	184 208 (26.3)
Gastrointestinal	2865	99 944 (14.2)
Neurological	2829	97 699 (13.9)
Metabolic/endocrine	1999	73 533 (10.5)
Bleeding/coagulation dysfunction	1800	68 545 (9.8)
Altered mental status	1898	68 075 (9.7)
Facial edema	1636	55 079 (7.9)
Respiratory	1557	54 089 (7.7)
Syncope/dizziness	1542	53 610 (7.6)
Cardiovascular	996	35 884 (5.1)
Psychological	859	29 048 (4.1)
Musculoskeletal	714	22 772 (3.2)
Injection site injury	552	16 274 (2.3)
Renal/genitourinary	417	17 101 (2.4)†
Peripheral edema	425	15 388 (2.2)
Ophthalmologic	413	14 013 (2.0)
Nonspecific symptoms	433	11 760 (1.7)
Infectious	306	10 346 (1.5)†
Otologic	92	3209 (0.5)
Exposure without adverse effect at time of evaluation	2035	50 031 (7.1)
Unspecified overdose/toxicity	1091	32 065 (4.6)
Unspecified or generalized allergic reaction	657	16 096 (2.3)
Unspecified effect	242	6621 (0.9)

*Conditions were not mutually exclusive; therefore, percentages may total >100%.
†Estimates with coefficient of variation >30%: renal/genitourinary conditions, 33.4% and infectious, 32.6%.

Table 3. Number of Cases and Annual Estimate of Individuals With Adverse Drug Events Treated in Emergency Departments by Event Type—United States, 2004-2005

	Overall		Hospitalizations*		
Adverse Drug Event†	Cases, No.	Annual Estimate, No. (%)	Cases, No.	Annual Estimate, No. (%)	Hospitalized, %
Allergic reactions	6890	235 202 (33.5)	375	13 232 (11.3)	5.6
Unintentional overdoses	7249	225 298 (32.1)	1919	62 607 (53.4)	27.8
Adverse effects	5846	200 887 (28.6)	1069	36 397 (31.0)	18.1
Secondary effects	669	24 371 (3.5)	102	4333 (3.7)	15.6
Vaccine reactions	644	15 790 (2.3)	22	751 (0.6)‡	4.8

*Hospitalizations include patients who were admitted to an inpatient unit of the health care facility, transferred to another health care facility, or held in the emergency department as observation admissions.
†Adverse events were categorized into 1 and only 1 of the following types: allergic reactions (immunologically mediated effects); adverse effects (undesirable pharmacologic or idiosyncratic effects at recommended doses); unintentional overdoses (toxic effects linked to excess dose or impaired excretion); vaccine reactions (adverse events specifically linked to a vaccine); or secondary effects (adverse events not due to allergic reactions, adverse effects, unintentional overdoses, or vaccines; eg, falls, choking).
‡Estimate of less than 1200 and coefficient of variation >30%: hospitalization for vaccine reactions, 50.6%. Proportion hospitalized was not calculated.

Table 4. Number of Cases and Annual Estimate of Individuals With Adverse Drug Events Treated In Emergency Departments by Drug Class—United States, 2004-2005

Therapeutic Category (Drug Class)*	Adverse Drug Events†	
	Cases	Annual Estimate, No. (%)
Central nervous system agents	4698	150 257 (21.4)
Opioid-containing analgesics	1167	41 421 (5.9)
Non–opioid-containing analgesics	715	20 887 (3.0)
Antidepressants and mood stabilizers	591	19 817 (2.8)
Anticonvulsants	588	17 887 (2.6)
Antipsychotics	443	13 635 (1.9)
Benzodiazepines	288	9299 (1.3)
Non–benzodiazepine-derived sedatives	182	6375 (0.9)
Stimulants	177	4152 (0.6)
Anesthetics	92	3176 (0.5)
Other central nervous system agents or central nervous system agents from different classes	455	13 608 (1.9)
Systemic antimicrobial agents	3867	127 807 (18.2)
Amoxicillin-containing agents	1150	35 228 (5.0)
Quinolones	445	16 074 (2.3)
Sulfonamide-containing agents	446	15 593 (2.2)
Cephalosporins	454	15 369 (2.2)
Erythromycins and macrolides	329	11 833 (1.7)
Penicillin	233	7848 (1.1)
Antivirals, antiparasitics, and antifungals	141	4338 (0.6)
Tetracyclines	106	3662 (0.5)
Lincomycins	100	3332 (0.5)
Metronidazole	59	1815 (0.3)
Other antimicrobial agents, unspecified antimicrobials, or drugs from different classes of antimicrobial agents	404	12 715 (1.8)
Hormone-modifying agents	2345	84 098 (12.0)
Insulins	1494	53 030 (7.6)
Oral hypoglycemic agents	374	14 528 (2.1)‡
Glucocorticoids	182	6575 (0.9)
Estrogens and progesterones	91	2588 (0.4)
Other hormone-modifying agents or drugs from different classes of hormone-modifying agents	204	7377 (1.1)
Hematologic and oncologic agents	2120	72 029 (10.3)
Anticoagulants	1045	36 110 (5.1)‡
Platelet inhibitors	407	17 258 (2.5)‡
Antineoplastic agents	481	12 129 (1.7)‡
Other hematologic and oncologic agents or drugs from different classes of blood-modifying agents	187	6532 (0.9)‡
Cardiovascular agents	1498	53 457 (7.6)
ACE inhibitors/ARBs	306	10 392 (1.5)
Lipid-lowering agents	214	8828 (1.3)
β-Blockers	189	6596 (0.9)
Digitalis glycosides	131	5318 (0.8)‡
Diuretics	142	5108 (0.7)
Calcium channel blockers	138	5004 (0.7)
Nitrates/antiarrhythmics	69	2582 (0.4)
Centrally acting antiadrenergics	82	2162 (0.3)
Other cardiovascular drugs or drugs from different classes of cardiovascular agents	227	7467 (1.1)

(continued)

tentional overdoses (53.4%; 95% CI, 46.9%-59.9%), while allergic reactions accounted for 11.3% (95% CI, 6.1%-16.4%). The estimated proportion of patients hospitalized following unintentional overdoses (27.8%; 95% CI, 22.3%-33.3%) was 5 times greater than the estimated proportion hospitalized due to allergic reactions (5.6%; 95% CI, 3.5%-7.7%).

Drugs that commonly require regular outpatient monitoring to prevent acute toxicity (antidiabetic agents, warfarin, several anticonvulsants, digitalis glycosides, theophylline, and lithium) were involved in most unintentional overdoses (3387 cases; annual estimate, 53.3%; 95% CI, 41.6%-64.6%). These drugs were implicated in 66.0% of estimated overdoses requiring hospitalization (1149 cases; 95% CI, 53.8%-78.2%) and 41.5% of all estimated hospitalizations (1381 cases; 95% CI, 30.9%-52.1%). Among patients aged 65 years or older, these drugs that commonly require regular monitoring were implicated in 85.4% of estimated overdose visits (1744 cases; 95% CI, 80.3%-90.5%), 87.0% of estimated overdoses requiring hospitalization (708 cases; 95% CI, 82.3%-91.7%), and 54.4% of all estimated hospitalizations (829 cases; 95% CI, 45.0%-63.7%).

In 94.0% of estimated ADE visits, a single drug (18 315 cases; annual estimate, 86.6%) or drugs from the same therapeutic category (1611 cases; annual estimate, 7.4%) were implicated. The most common drug categories and classes implicated are listed in TABLE 4 with ADEs involving drugs from more than 1 therapeutic category listed separately. Overall, the 5 most common drug classes implicated in ADEs were insulins, opioid-containing analgesics, anticoagulants, amoxicillin-containing agents, and antihistamines/cold remedies. They accounted for 27.7% of estimated ADEs (5780 cases; 95% CI, 24.0%-31.3%). The 5 most common classes implicated in hospitalized ADEs were anticoagulants, insulins, opioid-containing analgesics, oral hypoglycemic agents, and antineoplastic agents, and these drug classes

accounted for 38.4% of hospitalizations (1366 cases; 95% CI, 29.8%-46.9%).

Eighteen drugs were implicated alone or in combination with other drugs in 1% or more of estimated ADEs (TABLE 5). Insulins or warfarin, drugs that typically require ongoing monitoring to prevent overdose or toxicity, were implicated in 1 in every 7 estimated ADEs treated in EDs (14.1%; 95% CI, 9.6%-18.6%). Seven of these drugs were antibiotics, and together these antibiotics were implicated in 1 in every 8 estimated ADE treated in EDs (13.0%; 95% CI, 11.7%-13.3%). These 18 drugs were implicated in 44.6% of all estimated hospitalizations (1465 cases; 95% CI, 35.9%-53.2%). Insulin or warfarin was implicated in more than one quarter of all estimated hospitalizations (871 cases; 95% CI, 17.3%-35.2%) while the 7 antibiotics were implicated in only 3.8% of hospitalizations (121 cases; 95% CI, 2.7%-5.0%). Among patients aged 65 years or older, 3 drugs that typically require ongoing monitoring (insulin, warfarin, and digoxin) were implicated in 1 in every 3 estimated ADEs treated in EDs (1592 cases; 33.3%; 95% CI, 27.8%-38.7%) and 41.5% of estimated hospitalizations (646 cases; 95% CI, 32.4%-50.6%).

Table 4. Number of Cases and Annual Estimate of Individuals With Adverse Drug Events Treated In Emergency Departments by Drug Class—United States, 2004-2005 (cont)

Therapeutic Category (Drug Class)*	Adverse Drug Events†	
	Cases	Annual Estimate, No. (%)
Musculoskeletal agents	1043	35 177 (5.0)
Nonselective nonsteroidal anti-inflammatory drugs	727	23 394 (3.3)
Muscle relaxants	133	4616 (0.7)
COX-2 selective nonsteroidal anti-inflammatory drugs	101	4587 (0.7)
Other musculoskeletal drugs or drugs from different classes of musculoskeletal agents	82	2580 (0.4)
Antihistamines, decongestants, expectorants, antitussives, and combination cold remedies	924	28 403 (4.0)
Vaccines	641	15 911 (2.3)
Gastrointestinal agents	385	12 477 (1.8)
Diagnostic agents	256	9726 (1.4)
Dermatologic agents	283	9459 (1.3)
Herbs, dietary supplements, and alternative agents	262	9423 (1.3)
Therapeutic nutrients, vitamins, minerals, and electrolytes	254	8445 (1.2)
Topical eye, ear, nose, and throat agents	195	6408 (0.9)
Autonomic agents	148	4302 (0.6)
Respiratory tract agents	127	3812 (0.5)
Immune-modifying agents	116	3654 (0.5)
Other agents	114	4547 (0.6)
Drugs not stated or not known	650	20 022 (2.9)
Drugs from more than 1 therapeutic category	1372	42 136 (6.0)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; COX, cyclooxygenase.
*For 18 315 cases (annual estimate, 607 245; 86.6%) a single drug was implicated in the adverse event. For 1611 cases (annual estimate, 52 167; 7.4%) drugs from the same therapeutic category were implicated. For the remaining cases drugs from more than 1 therapeutic category were implicated and these are listed in a separate category.
†Annual estimates and percentages may not total 100% due to rounding.
‡Estimates with coefficient of variation >30%: oral hypoglycemic agents, 31.1%; anticoagulants, 33.3%; platelet inhibitors, 32.2%; antineoplastic agents, 36.3%; other hematologic and oncologic agents or drugs from different classes of blood-modifying agents, 33.8%; and digitalis glycosides, 33.5%.

COMMENT

Based on data from a nationally representative surveillance system, we estimate that more than 700 000 patients were treated for ADEs in US EDs annually in 2004 and 2005, and 1 of every 6 required subsequent hospital admission, transfer to another health care facility, or ED observation admission. Individuals aged 65 years or older were more than twice as likely to be treated in EDs for an ADE and nearly 7 times as likely to require hospitalization as individuals younger than 65 years. Among all patients who were hospitalized, most ADEs were due to unintentional overdoses and two thirds of these were due to toxicity from a relatively small set of drugs for which regular monitoring is commonly required to prevent acute toxicity. Sixteen of the 18 drugs most commonly causing ADEs have been in clinical use for more than 20 years.[20]

These population-based surveillance data help define the national scope of the outpatient ADE problem, underscore the need for intensified prevention efforts, and identify areas in which to focus interventions for the greatest public health impact. The finding that individuals aged 65 years or older (12% of the US population) accounted for one quarter of ADEs overall and half of adverse events requiring hospitalization highlights the importance of directing ADE prevention efforts to this vulnerable population. Emergency department visits for ADEs in this age group were nearly as common as those for motor vehicle occupant injuries.[21]

Important underlying factors contribute to the disproportionate effect of ADEs on individuals aged 65 years or older (eg, greater frequency and number of drugs used by this age group, age-related physiologic changes). However, the finding that just 3 drugs (warfarin, insulin, and digoxin), with narrow therapeutic index and high risk of overdose or toxicity, caused nearly one third of ED-treated ADEs in patients aged 65 years or older provides further focus for prevention efforts. A recent study found that high proportions of ambulatory patients taking drugs with a narrow therapeutic range had no serum concentration monitor-

Table 5. Number of Cases and Annual Estimate of Drugs Most Commonly Implicated in Adverse Events Treated in Emergency Departments—United States, 2004-2005*

Drug	Adverse Drug Events	
	Cases, No.	Annual Estimate, No. (%)
Insulins	1577	55 819 (8.0)
Warfarin	1234	43 401 (6.2)†
Amoxicillin	1022	30 135 (4.3)
Aspirin	473	17 734 (2.5)
Trimethoprim-sulfamethoxazole	447	15 291 (2.2)
Hydrocodone-acetaminophen	420	15 512 (2.2)
Ibuprofen	526	14 852 (2.1)
Acetaminophen	497	12 832 (1.8)
Clopidogrel	241	10 931 (1.6)†
Cephalexin	293	10 628 (1.5)
Penicillin	270	9275 (1.3)
Amoxicillin-clavulanate	274	8959 (1.3)
Azithromycin	255	8794 (1.3)
Levofloxacin	230	8682 (1.2)
Naproxen	245	8634 (1.2)
Phenytoin	238	7937 (1.1)
Oxycodone-acetaminophen	227	7328 (1.0)
Metformin	179	6678 (1.0)

*Drugs implicated in ≥1% of adverse events. For 434 cases (annual estimate, 15 784 [2.2%]) 2 of these 18 drugs were implicated in the adverse event. Therefore, these 18 drugs accounted for adverse drug events in 8214 cases (annual estimate, 277 636 [39.6%]).
†Estimates with coefficient of variation >30%: warfarin, 32.5%; clopidogrel, 36.6%.

ing during 1 year of use.[22] Other safety interventions designed to prevent these specific ADEs, such as patient education programs, patient self-management, and specialist management, have long been available but use of these interventions varies.[23] The data from our study emphasize the national scope of the adverse health outcomes due to outpatient ADEs that could be addressed through targeted implementation of current safety interventions.

We compared the magnitude of ADEs to the public health burden of unintentional injuries because an injury-oriented approach provides a valuable framework for understanding and preventing a wide range of harmful events.[24] Other unintentional injuries once considered unavoidable have been greatly reduced in frequency and severity using injury prevention techniques. Examples include reduction of motor vehicle–related injury with enforcement of speed limits[25] and installation of airbags,[26] reduction of needlestick injuries in health care workers with introduction of needle protective devices,[27] and reduction in unintentional overdose deaths after implementing requirements for child-resistant packaging.[28] Considering outpatient ADEs as an interaction of an agent (drug), a host (patient), and the environment (physical and social) can help conceptualize injury-based approaches for preventing or ameliorating outpatient ADEs.[29]

The population-based surveillance data we report are consistent with findings from studies in single institutions,[30,31] studies in Medicare enrollees,[23] and contention of drug safety analysts that a large proportion of the public health burden of ADEs is attributable to "older drugs, used poorly."[32] Direct comparisons between surveillance data from NEISS-CADES and previous reports on outpatient ADEs are limited by differences in case definitions and outcomes evaluated. For example, some ED-based studies have included drug abuse, suicide attempts, noncompliance or nonadherence, therapeutic failures of drugs or inadequate drug therapy, and adverse events from drugs given during ED visits.[33] Other studies of outpatient ADEs have measured a range of outcomes including patient self-reported symptoms,[34] potential ADEs,[35] and assessments of severity.[31] Nevertheless, studies of single EDs[30] and studies of ADEs in a local Medicare population[36] have found similar types of adverse effects and implicated many of the same drugs and drug classes. Zhan et al[37] recently analyzed data from one source of nationally representative outpatient ADE data, the National Hospital Ambulatory Medical Care Survey (NHAMCS), and reported a similar rate of ED visits for ADEs (1.9 to 2.8 per 1000 for 1995 through 2001). However, this analysis was limited to pooled data for a 6-year study period to describe patient characteristics and broad drug categories based on *International Classification of Diseases* coding.

NEISS-CADES has several advantages compared with other sources of ADE information. Because NEISS-CADES collects data from a nationally representative sample of hospital EDs, data are not subject to the questions of generalizability as are data collected from single institutions or single geographic areas.[30] Moreover, compared with many research studies and population surveys, NEISS-CADES data collection is timely, with preliminary data typically available within several weeks of the ED visit.[13] NEISS-CADES data collection is ongoing, enabling trend monitoring and evaluation of national safety interventions not possible with research studies that typically have defined study periods. In addition, although NEISS-CADES recently began operation, it will likely be less susceptible than voluntary reporting systems to variations in reporting rates over time,[38] just as the parent surveillance system, NEISS, has produced stable estimates of consumer product-related injuries for more than 3 decades.[19,39]

Adverse drug event surveillance with NEISS-CADES has several limitations that likely result in an underestimate of the outpatient ADE burden. First, NEISS-CADES is restricted to ED patients. Cases of ADEs diagnosed and treated in other settings (eg, primary care offices, non–hospital-based urgent care centers, or directly admitted to hospitals) or not treated in any health care facility will not be captured.

Second, some ADEs that lead to ED visits, such as effects of chronic drug exposure, adverse effects manifested by the gradual onset of symptoms, and uncommon adverse effects, may be unrecognized by ED physicians and therefore may be undetected.

Third, because NEISS-CADES relies on documentation of ADEs by the treating physician, it is likely less sensitive than research studies involving chart review by specially trained pharmacists or physicians, computer-generated signals, patient interview, or combination approaches to identify undiagnosed or unreported ADEs.[40]

Fourth, NEISS-CADES could be biased toward detecting acute, well-

known drug effects or effects for which testing is available in the ED, such as hypoglycemia from insulin overdose or hypocoagulability due to warfarin. However, in an evaluation of 6 NEISS-CADES hospitals, these events were found to be underreported rather than overreported. Excluding these events improved the sensitivity of ADE identification from 33% to 45%.[14] However, the weighted positive predictive value in this evaluation for coder-reported ADEs was 92%.[14] Although this estimate of sensitivity for 6 of the participating hospitals may appear low, it is considerably higher than voluntary reporting, which often captures less than 1% of serious adverse reactions and rarely captures more than 10%.[38] Efforts to improve the sensitivity of ADE identification are part of the ongoing NEISS-CADES quality assurance process, and reassessments of ADE identification are planned.

And fifth, while ADE surveillance with NEISS-CADES provides information on outpatient ADEs treated in EDs, the NEISS-CADES data are insufficient to provide a complete perspective on outpatient ADEs. For instance, we did not estimate the total number of fatalities from outpatient ADEs because NEISS-CADES does not capture prehospital deaths or deaths in the ED. Moreover, although calculating the proportion of ADEs relative to that drug's use can provide information on relative risks for comparison with other drugs, we did not report such calculations because estimates of national outpatient drug use are not available from NEISS-CADES data. In addition, we did not attempt to categorize ADEs by "preventability" or the presence of a medication "error" in this investigation. Further examination of the data collected through this ED-based public health surveillance system is needed to determine if the clinical details are available for such categorization.

We expected national estimates of uncommon events (eg, estimates of <1200 per year or estimates based on fewer than 20 cases) to have CVs greater than 30%; however, several national estimates of ADE estimates were based on relatively large numbers of cases but also had CVs greater than 30% (eg, warfarin with 1234 cases, CV=32.5%). This situation can occur for estimates generated from a probability sample, such as NEISS, when the underlying distribution of the condition under surveillance is not evenly distributed across the population. For example, NEISS estimates of ED visits for snow-skiing injuries have elevated CVs because hospitals in mountainous northern states have high numbers of visits for these injuries while hospitals in coastal southern states have low numbers of visits.

Drug selection,[41-43] disease monitoring,[44,45] therapeutic outcomes,[46] and adverse outcomes[47] have all been shown to vary by hospital and geographic area. These variations in clinical practice likely contribute to variation in the number of ADEs treated at NEISS hospitals, resulting in CVs greater than 30% for some estimates presented in this study. A recent systematic review reported that anticoagulation control varied extensively among study settings,[48] so it is not unreasonable that adverse events from anticoagulants might vary among the catchment areas served by NEISS hospitals. Other possible explanations for elevated CVs include variability in the level of detail in clinical documentation or variability in data collection across NEISS hospitals. Because ADEs are typically underdocumented,[40] and an evaluation of NEISS-CADES data collection found a high positive predictive value,[14] variability due to documentation or data collection practices would likely increase these national estimates.

Efforts to reduce the burden of outpatient ADEs have been hampered by sparse data, except in selected health care systems or settings.[3] Ongoing data collection in NEISS-CADES will enable more detailed examination of the epidemiology of ED-treated outpatient ADEs, focusing on specific patient populations, drug classes, conditions, and circumstances. Identifying appropriate measures of drug exposure and evaluating drug risks in relation to drug benefits remain important challenges in improving the quality of outpatient drug therapy. In the future, data from electronic health records may provide national, real-time data on outpatient drug safety.[40] Until then, leveraging existing public health surveillance systems provides a feasible, cost-efficient way to monitor the national health burden of outpatient drug safety problems and helps target prevention strategies tailored to the specific events of greatest population burden.

Author Contributions: Dr Budnitz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Budnitz, Pollock, Schroeder.
Acquisition of data: Budnitz, Weidenbach, Schroeder, Annest.
Analysis and interpretation of data: Budnitz, Pollock, Weidenbach, Mendelsohn, Schroeder.
Drafting of the manuscript: Budnitz, Pollock, Weidenbach.
Critical revision of the manuscript for important intellectual content: Budnitz, Mendelsohn, Schroeder, Annest.
Statistical analysis: Budnitz, Weidenbach, Mendelsohn, Schroeder, Annest.
Obtained funding: Budnitz.
Administrative, technical, or material support: Budnitz, Weidenbach, Schroeder.
Study supervision: Budnitz, Pollock.
Financial Disclosures: Dr Mendelsohn contributed to this research while he was a CDC Epidemic Intelligence service officer assigned to the Office of Drug Safety, FDA. Financial support was solely through his US government salary. Dr Mendelsohn is now director of epidemiology at MedImmune Inc. None of the products marketed by MedImmune, nor competitors' products, are specifically addressed in this article. None of the other authors reported financial disclosures.
Funding/Support: This work was implemented by CDC, FDA, and US Consumer Product Safety Commission (CPSC) scientists. CDC provided funding for the study and FDA provided funding for medical coding of the data using MedDRA terms and analyses.
Role of the Sponsors: The CDC provided funding for the design and conduct of the investigation; data collection, management, analysis, and interpretation; and preparation and review of the manuscript.
Disclaimer: The findings and conclusions in this article are those of the authors and do not necessarily represent the views of CDC, FDA, or the CPSC.
Acknowledgment: We thank Steve Brown, MD, of the US Department of Veterans Affairs for providing the National Drug File Reference Terminology; Terri Nelson, BA, of the US CPSC and Shelley Elbert, MA, formerly of CPSC for their assistance with data collection; Cathy Irish, BS, of CPSC and Jacqui Butler, MPA, of the CDC for technical support; Benjamin Kupronis, MPH, and Tadesse Haileyesus, MS, of CDC for programming assistance; and Art McDonald, MPhil, formerly of CPSC and Anne Trontell, MD, from the FDA for assistance in study design and conceptualization. No individuals named herein received compensation for their contributions.

REFERENCES

1. Slone Epidemiology Center. Patterns of medication use in the United States, 2004: a report from the Slone Survey. http://www.bu.edu/slone/SloneSurvey/AnnualRpt/SloneSurveyReport2004.pdf. Accessed September 2005.

2. Bates DW. Drugs and adverse drug reactions: how worried should we be? *JAMA*. 1998;279:1216-1217.

3. *Adverse Drug Events: The Magnitude of Health Risk Is Uncertain Because of Limited Incidence Data.* Washington, DC: General Accounting Office; 2000.

4. Tierney WM. Adverse outpatient drug events: a problem and an opportunity. *N Engl J Med*. 2003;348:1587-1589.

5. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med*. 2003;348:1556-1564.

6. Centers for Medicare & Medicaid Services. Toolkit for health care professionals: Medicare prescription drug coverage materials for you, your staff and Medicare patients. http://www.cms.hhs.gov/MLNProducts/23_drugcoverage.asp. Accessed December 2005.

7. Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events: ADE Prevention Study Group. *JAMA*. 1995;274:35-43.

8. 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;277:301-306.

9. Classen D. Medication safety: moving from illusion to reality. *JAMA*. 2003;289:1154-1156.

10. *National Electronic Injury Surveillance System All Injury Program Sample Design and Implementation.* Washington, DC: US Consumer Product Safety Commission; 2002.

11. Consumer Product Safety Act, 15 USC §2051-2084 (1972).

12. Vervloet D, Durham S. Adverse reactions to drugs. *BMJ*. 1998;316:1511-1514.

13. Budnitz DS, Pollock DA, Mendelsohn AB, et al. Emergency department visits for outpatient adverse drug events: demonstration for a national surveillance system. *Ann Emerg Med*. 2005;45:197-206.

14. Centers for Disease Control and Prevention. Assessing the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project—six sites, United States, January 1-June 15, 2004. *MMWR Morb Mortal Wkly Rep*. 2005;54:380-383.

15. ICH Points to Consider Working Group. *MedDRA Term Selection: Points to Consider Release 3.2 Based on MedDRA version 6.1.* Geneva, Switzerland: ICH Secretariat; 2003.

16. Carter JS, Brown SH, Erlbaum MS, et al. Initializing the VA medication reference terminology using UMLS metathesaurus co-occurrences. *Proc AMIA Symp*. 2002:116-120.

17. Population Division; US Census Bureau. Table 2: Annual estimates of the population by selected age groups and sex for the United States: April 1, 2000 to July 1, 2004. http://www.census.gov/popest/national/asrh/NC-EST2005/NC-EST2005-02.xls. Accessed July 2006.

18. Population Division; US Census Bureau. Table 1: Annual estimates of the population by sex and five-year age groups for the United States: April 1, 2000 to July 1, 2005. http://www.census.gov/popest/national/asrh/NC-EST2005/NC-EST2005-01.xls. Accessed July 2006.

19. Schroeder T, Ault K. *National Electronic Injury Surveillance System (NEISS) Sample Design and Implementation From 1997 to Present.* Washington, DC: US Consumer Product Safety Commission; 2001.

20. Centers for Education and Research on Therapeutics (CERTs) Risk Assessment Workshop Participants. Risk assessment of drugs, biologics and therapeutic devices: present and future issues. *Pharmacoepidemiol Drug Saf*. 2003;12:653-662.

21. Centers for Disease Control and Prevention. Web-based Injury Statistics Query and Reporting System (WISQARS). National Center for Injury Prevention and Control, Centers for Disease Control and Prevention; 2005. http://www.cdc.gov/ncipc/wisqars/default.htm. Accessed December 2005.

22. Raebel MA, Carroll NM, Andrade SE, et al. Monitoring of drugs with a narrow therapeutic range in ambulatory care. *Am J Manag Care*. 2006;12:268-274.

23. Shojania KG, Duncan BW, McDonald KM, et al. Making health care safer: a critical analysis of patient safety practices. *Evid Rep Technol Assess (Summ)*. 2001;43:87-99.

24. Layde PM, Cortes LM, Teret SP, et al. Patient safety efforts should focus on medical injuries. *JAMA*. 2002;287:1993-1997.

25. Richter ED, Berman T, Friedman L, Ben-David G. Speed, road injury, and public health. *Annu Rev Public Health*. 2006;27:125-152.

26. Graham JD, Thompson KM, Goldie SJ, et al. The cost-effectiveness of air bags by seating position. *JAMA*. 1997;278:1418-1425.

27. Trim JC, Elliott TS. A review of sharps injuries and preventative strategies. *J Hosp Infect*. 2003;53:237-242.

28. Rodgers GB. The safety effects of child-resistant packaging for oral prescription drugs: two decades of experience. *JAMA*. 1996;275:1661-1665.

29. Budnitz DS, Layde PM. Outpatient drug safety: new steps in an old direction [published online ahead of print April 24, 2006]. *Pharmacoepidemiol Drug Saf*. doi:10.1002/pds.1242.

30. Hafner JWJ, Belknap SM, Squillante MD, Bucheit KA. Adverse drug events in emergency department patients. *Ann Emerg Med*. 2002;39:258-267.

31. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA*. 2003;289:1107-1116.

32. Electronic Orange Book. FDA, Center for Drug Evaluation and Research; 2005. http://www.fda.gov/cder/ob/default.htm. Accessed December 2005.

33. Zed P. Drug-related visits to the emergency department. *J Pharm Pract*. 2005;18:329-335.

34. Weingart SN, Gandhi TK, Seger AC, et al. Patient-reported medication symptoms in primary care. *Arch Intern Med*. 2005;165:234-240.

35. Gandhi TK, Weingart SN, Seger AC, et al. Outpatient prescribing errors and the impact of computerized prescribing. *J Gen Intern Med*. 2005;20:837-841.

36. Field TS, Gurwitz JH, Harrold LR, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. *J Am Geriatr Soc*. 2004;52:1349-1354.

37. Zhan C, Arispe I, Kelley E, et al. Ambulatory care visits for treating adverse drug effects in the United States, 1995-2001. *Jt Comm J Qual Patient Saf*. 2005;31:372-378.

38. Ahmad SR, Goetsch RA, Marks NS. Spontaneous reporting in the United States. In: Strom BL, ed. *Pharmacoepidemiology*. 4th ed. West Sussex, England: John Wiley & Sons Ltd; 2005:153.

39. Schroeder T, Ault K. *National Electronic Injury Surveillance System (NEISS) Sample Design and Implementation From 1979 to 1996.* Washington, DC: US Consumer Product Safety Commission; 2001.

40. Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. *Qual Saf Health Care*. 2004;13:306-314.

41. O'Connor GT, Quinton HB, Traven ND, et al. Geographic variation in the treatment of acute myocardial infarction: the Cooperative Cardiovascular Project. *JAMA*. 1999;281:627-633.

42. Dubois RW, Batchlor E, Wade S. Geographic variation in the use of medications: is uniformity good news or bad? *Health Aff (Millwood)*. 2002;21:240-250.

43. Lopez J, Meier J, Cunningham F, Siegel D. Antihypertensive medication use in the Department of Veterans Affairs: a national analysis of prescribing patterns from 2000 to 2002. *Am J Hypertens*. 2004;17:1095-1099.

44. Havranek EP, Wolfe P, Masoudi FA, Rathore SS, Krumholz HM, Ordin DL. Provider and hospital characteristics associated with geographic variation in the evaluation and management of elderly patients with heart failure. *Arch Intern Med*. 2004;164:1186-1191.

45. Jencks SF, Cuerdon T, Burwen DR, et al. Quality of medical care delivered to Medicare beneficiaries: a profile at state and national levels. *JAMA*. 2000;284:1670-1676.

46. Krumholz HM, Chen J, Rathore SS, Wang Y, Radford MJ. Regional variation in the treatment and outcomes of myocardial infarction: investigating New England's advantage. *Am Heart J*. 2003;146:242-249.

47. Booth GL, Hux JE, Fang J, Chan BT. Time trends and geographic disparities in acute complications of diabetes in Ontario, Canada. *Diabetes Care*. 2005;28:1045-1050.

48. van Walraven C, Jennings A, Oake N, et al. Effect of study setting on anticoagulation control: a systematic review and metaregression. *Chest*. 2006;129:1155-1166.

