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Adverse Drug Events in the Outpatient Setting: An 11-Year National Analysis

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Abstract

Purpose—Adverse drug events (ADEs) are a common complication of medical care resulting in high morbidity and medical expenditure. Population level estimates of outpatient ADEs are limited. Our objective was to provide national estimates and characterizations of outpatient ADEs and determine risk factors associated with these events.

Methods—Data are from the National Center for Health Statistics which collects information on patient visits to outpatient clinics and emergency departments throughout the United States. We examined visits between 1995 and 2005 and measured the national annual estimates of and risk factors for outpatient ADEs requiring medical treatment.

Results—The national annual number of ADE-related visits was 4,335,990 (95%CI, 4,326,872–4,345,108). Visits for ADEs to outpatient clinics increased over the study period from 9.0 to 17.0 per 1000 persons (*P* value for trend<0.001). In multivariate analyses, factors associated with ADE visits included patient age (OR 2.13; 95%CI 1.63–2.79 for 65 years and older), number of medications taken by patient (OR, 1.88; 95%CI, 1.58–2.25 for five medications or more), and female gender (OR, 1.51; 95%CI, 1.34–1.71). Overall, outpatient ADEs resulted in 107,468 (95%CI, 89,011–125,925) hospital admissions annually, with older patients at highest risk for hospitalization (*P* value for trend<0.001).

Conclusions—Both patient age and polypharmacy use are risk factors for ADE-related healthcare visits, which have substantially increased in outpatient clinics between 1995 and 2005. The incidence of ADEs has particularly increased among patients 65 years and older with as many as 1 in 20 persons seeking medical care for an ADE.

Keywords

Adverse drug events; outpatients; polypharmacy

INTRODUCTION

Adverse drug events (ADEs) are a common and costly complication of medical care. As many as 4.6% of deaths in the United States may be the result of an ADE, making ADEs one of the top 5 leading causes of death (1). Among hospitalized patients, an estimated 6.5% of patients experience an ADE with an almost 2-fold increased risk of death in this population (2,3). The cost of ADEs to our medical system is substantial, with high rates of ADE-related admissions (1,4,5), prolonged hospital stays, and increased resource utilization while hospitalized (2,3,6).

In the outpatient setting, more than 80% of adults in the U.S. report using at least 1 medication and approximately 70% of outpatient clinic visits are associated with the prescription or continuation of a medication (7,8). While medication use is highest among older patients, rates among younger persons are high as well with 82% of adults 18 to 44 years old reporting use of at least one medication during the preceding week and nearly 52% using a prescription medication (7,9).

Despite the prevalence of outpatient medication treatment, patterns and rates of ADEs occurring in the ambulatory population are not well-defined and little is known about the healthcare utilization associated with these events. Studies examining the incidence of outpatient ADEs have been conducted in select patient groups and do not provide a comprehensive picture of the scope of ADEs in the outpatient setting (10–12). A recent national study found that more than 700,000 patients are treated in emergency departments annually for ADEs, accounting for 2.5% of all emergency department visits for unintentional injuries (13). It is likely that a large number of outpatients experiencing an ADE also seek care in outpatient clinics where the majority of medications are prescribed and therapeutic effects monitored (14).

Using data from a national survey over an 11-year period, we provide population estimates of the annual incidence of outpatient ADEs requiring medical treatment in the U.S. We also provide estimates of ADE trends over time and risk factors for ADEs resulting in a healthcare visit.

METHODS

Data Sources

The National Ambulatory Medical Care Survey (NAMCS) and the National Hospital and Ambulatory Medical Care Survey (NHAMCS) from 1995 to 2005 provide data on individuals seeking medical care for ADEs in outpatient clinics and emergency departments (15). These surveys are conducted annually by the National Center for Health Statistics (NCHS), a branch of the Centers for Disease Control and Prevention, and include nationally representative probability samples of patient visits to office-based clinics, hospital outpatient clinics, and emergency departments. Data from these surveys are weighted to produce national estimates of the utilization of ambulatory medical care in the United States.

The NAMCS surveys patient visits to non-federally employed physicians principally engaged in office-based patient care. A 3-stage probability design is used consisting of geographic areas, physician practices within these areas, and patient visits within practices. Physicians are randomly assigned a 1-week reporting period during which data are collected on a systematic random sample of visits using a standard patient record form. Patient visits included in the NHAMCS are visits to hospital-based clinics and emergency departments of non-institutional general and short-stay hospitals, exclusive of Federal, military, and Veterans Administration hospitals. The NHAMCS uses a 4-stage probability design

consisting of geographic areas, hospitals within these areas, clinics or emergency departments within hospitals, and patient visits to clinics or emergency departments. A systematic, random sample of patient visits to the selected clinics and emergency departments are surveyed during a randomly assigned 4-week reporting period.

Forms include data on patient demographics and details of the visit including up to three reasons for the visit (coded according to the NCHS *Reason for Visit Classification*), diagnostic and screening services provided, treatments and procedures performed, medications prescribed or provided at the visit, up to three physician's diagnoses for the visits (coded according to the *International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM]*), and disposition. In addition, surveys collect data on whether the visit is related to adverse effects of medical treatment, including adverse drug events, and these data are used by the NCHS to assign up to three *Supplementary Classification of External Causes of Injury and Poisoning Codes (E-Codes)* found in the ICD-9-CM. These codes permit more detailed classification of the diagnoses or conditions provided with the ICD-9-CM codes and include codes for medication groups implicated in ADEs, such as "penicillins" or "insulins and antidiabetic agents". Beginning in 1997, verbatim text description of the event is included in the public use file in addition to the E-Codes. In 2005, this survey item was modified in the clinic patient record forms and replaced with a question asking whether the visit was related to the adverse effect of medicinal/surgical care or a medicinal drug, without the inclusion of a text description.

Forms are reviewed for completeness by field representatives and are subject to detailed manual review upon receipt at the NCHS. Quality control for the medical and drug coding and straight-key items involves a two-way independent verification procedure of 10% of the records and all forms with differences in medical or drug coding or illegible entries are further reviewed and adjudicated. For items that required medical coding, error rates averaged less than 2% for the NAMCS and less than 3% for the NHAMCS (15).

Inclusion Criteria and Definitions

The study sample consisted of outpatient visits to office- and hospital-based clinics and all visits to emergency departments. ADEs were defined as injuries resulting from the use of prescription and over-the-counter medications for medical intervention (2,12), which includes adverse drug reactions and medication errors and excludes administration of the wrong medication (e.g. a child ingesting a family member's medication), intentional overdoses (e.g. a person ingesting medication with the intent of self-harm), or use of illicit substances. We included cases with E-Codes falling under "Drugs, Medicinal, and Biological Substances Causing Adverse Effects in Therapeutic Use" (E-Codes E930–E949), as well as cases with a diagnosis of an ADE, including anaphylactic shock (ICD-9-CM code 995.0), unspecified adverse effect of medicinal substance (ICD-9-CM code 995.2), shock due to anesthesia (ICD-9-CM code 995.4), aspirin gastritis (ICD-9-CM code 535.4), drug dermatitis (ICD-9-CM codes 692.3 and 693.0), drug reaction in newborn (ICD-9-CM code 779.4), drug psychoses (ICD-9-CM codes 292.1 through 292.9), and neuropathy due to drugs (ICD-9-CM 357.6). Patient visits with an adverse medical event of accidental poisoning by drugs (E-Codes E850–E858) or a diagnosis of poisoning by drugs (ICD-9-CM codes 960–979) were classified as an ADE visit if the verbatim text was available for review and met inclusion criteria. All cases associated with an adverse medical event code or diagnosis of drug dependence or abuse, use of an illicit substance, drug withdrawal, intentional self-harm, or assault by poisoning were excluded.

Data Analysis

We calculated yearly incidences of visits for ADEs to outpatient clinics and emergency departments per 1000 persons in the U.S. over the 11-year study period. The epidemiology of ADEs was described in terms of patient characteristics and medications implicated. Mean national annual estimates of ADEs were determined for each of these categories.

We identified up to three medications implicated in ADE visits through the adverse medical event codes and diagnoses. Medications were grouped into medication classes based on the *National Drug Code Directory*. In order to control for population exposure to different medications, ADE visit rates were calculated by dividing the number of ADE visits for each medication class by the number of outpatient visits in which a medication in the corresponding medication class was listed as part of the patient's therapy, including medications that were initiated or continued at the time of the visit. ADE cases with missing medication data were imputed for the calculation of ADE visit rates, assuming that the proportion of cases in each medication class was the same as the proportion of cases without missing data.

Statistical Analysis

Analyses were performed with SUDAAN statistical software (version 9.0.1; Research Triangle Institute, Research Triangle Park, NC), which is recommended by the NCHS for the computation of standard errors (SEs) in order to account for the multi-stage sampling design used in the NAMCS and NHAMCS. All estimates were based on 30 sample records or more and had relative SEs of 30% or less (i.e. the SE was no more than 30% of the estimate), as the NCHS considers estimates based on fewer records or with a greater SE unreliable.

Mean annual estimated numbers of ADEs were calculated with 95% confidence intervals (CIs) using yearly U.S. Bureau of the Census post-censal estimates of the civilian non-institutionalized population (16). We used linear trend tests to assess for change in the number of ADEs and use of polypharmacy over the 11-year study period and change in number and admission rates with increasing patient age. Multivariate logistic regression analysis was performed to identify factors associated with risk of ADEs. Variables used in the model included year of ADE visit, age, gender, race/ethnicity, number of medications patient was taking at the time of the ADE visit, payment source, and geographical region. Visits to clinic and emergency department settings were compared using χ^2 analyses; all test statistics were two-sided with *P* values considered statistically significant at an alpha-level of 0.05. Conditional probability rules were used to account for imputations in variance estimates of total ADE visits.

RESULTS

The estimated national annual number of ADE-related visits was 3,544,908 (CI, 3,162,667–3,927,149) in outpatient clinics and 791,082 (CI, 721,352 – 860,812) in emergency departments between 1995 and 2005 (based on 1960 and 2409 visit records to clinics and emergency departments, respectively). The population incidence of visits for ADEs to outpatient clinics increased from 9.1 per 1000 persons (CI, 6.6– 11.6) in 1995 to 16.9 per 1000 persons (CI, 12.2–21.6) in 2005 (*P* value for trend<0.001) (Figure 1, A). The incidence of ADE-related visits to emergency departments remained stable.

The mean annual population incidence of ADE visits to clinic and emergency department settings combined was 15.5 per 1000 persons (CI, 14.0–17.0) and increased with age (*P* value for trend <0.001) (Figure 1, B). Comparing the two time periods 1995 to 2000 and 2001 to 2005, the mean incidence of ADE visits was higher during the more recent time

period (13.2 per 1000 persons [CI, 11.5–14.9] vs. 18.1 per 1000 persons [CI, 15.6–20.5]). There was also an increase in the incidence of ADE visits among patients 65 years and older from 32.7 ADE visits per 1000 persons (CI, 26.9–38.6) to 48.8 ADE visits per 1000 persons (CI, 39.1–58.5), indicating that in recent years the incidence of ADE visits may be as high as 1 in 20 persons in this age group.

ADEs accounted for 0.4% of all visits to outpatient clinics with increasing proportions among older patient groups (Table 1). The majority of outpatient clinic visits for ADEs were by women (59.9%; CI, 56.0%– 63.7%), persons who were non-Hispanic white (78.5%; CI, 74.6%– 81.9%), those with private insurance (57.9%; CI, 53.6%– 62.1%), and those residing in the South (30.1%; CI 25.1%– 35.5%).

In the emergency department, ADEs led to 0.8% of all visits. In this setting, the highest proportion of ADE visits were comprised by patients 18 to 44 years old (39.8%; CI, 37.3%– 42.4%), although the proportion of ADE visits was highest among persons aged 65 years and older where they accounted for 1.2% of all emergency department visits. Overall, there was a significant difference in the age distribution of patients seeking care in emergency departments versus outpatient clinics ($p < 0.001$). As in the outpatient clinics, the majority of ADE visits were by women (64.8%; CI, 62.2%– 67.2%) and persons who were non-Hispanic white (71.1%; CI, 68.0%– 74.1%), had private insurance (49.1%; CI, 46.2%– 52.0%), and resided in the South (34.0%; CI, 29.9%– 38.4%).

The proportion of patients taking three or more medications increased over the study period (P value < 0.001 for 3 to 4 medications and 5 or more medications) and multivariate analysis revealed an increased risk for an ADE visit with increasing number of medications taken by patients (odds ratio [OR], 1.45; CI, 1.25–1.58 for 3 to 4 medications; OR, 1.88; CI, 1.58–2.25 for 5 or more medications) (Figure 2, Table 2). Other factors significantly associated with an ADE visit included increasing age group and female gender.

Medications implicated in ADEs are listed in Table 3. Overall, 96.4% of cases were related to a single medication class. Antimicrobial agents were most frequently implicated with an ADE (14.0%, CI 12.0%– 16.4%), followed by hormones and synthetic substitutes (11.4%, CI 9.2%– 14.0%) and cardiovascular agents (10.9%, CI 8.7%– 13.3%). The most common medication classes resulting in a clinic visit for an ADE were antihypertensives, estrogen/progesterones, non-opioid-based analgesics/antipyretics, and antidepressants and mood stabilizers. In the emergency department, the medication class of non-opioid-based analgesics/antipyretics was most frequently resulted in an ADE, followed by penicillins, sulfonamides, and insulin/hypoglycemic agents. The highest proportion of ADE visits resulting in hospital admission were related to cardiotonic glycosides (i.e. digoxin) (12.8%; CI, 8.6%– 18.6%), anticoagulants (11.2%; CI, 7.5%– 16.3%), anticonvulsants (7.0%; CI, 4.4%– 11.1%), and antineoplastics (6.5%; CI, 3.7%– 11.2%).

Rates of ADE visits—defined as number of ADE visits per 1000 outpatient visits associated with medication therapy—varied significantly for the different medication classes and are shown in Table 4. Aside from antineoplastic and immunosuppressive agents (12.9 ADE visits per 1000 medication visits, CI 7.8–21), medication classes with the highest ADE visit rates included hormones and synthetic substitutes (6.8 ADE visits per 1000 medication visits, CI 5.3–8.8), antimicrobial agents (6.6 ADE visits per 1000 medication visits, CI 5.4–8.0), and cardiovascular agents (4.8 ADE visits per 1000 medication visits, CI 3.7–6.2). Among antimicrobial agents, sulfonamides resulted in a significantly higher rate of ADEs than penicillins, macrolides, cephalosporins, and quinolones. Medications with ADE visit rates less than 2 per 1000 medication visits included gastrointestinal agents, antihistamines, cold remedies, and respiratory agents, and agents primarily affecting muscles.

Overall, outpatient ADEs resulted in a mean yearly total of 107,468 (CI, 89,011– 125,925) hospital admissions. In the emergency department, 0.63% (CI, 0.56%– 0.72%) of all visits requiring hospital admission were related to an ADE. Rates of admission for emergency department ADE visits increased significantly with increasing age, with admission rates of 4.1% (CI, 1.8%– 9.1%) among children 4 years old and younger, 6.1% (CI, 3.4%– 10.8%) for children 5 to 17 years old, 5.8% (CI, 4.2%– 7.9%) for adults 18 to 44 years old, 15.8% (CI, 12.0%– 19.0%) for adults 45 to 64 years old, and 24.9% (CI, 20.2%– 30.2%) for adults 65 years and older (p-value for trend trend<0.001).

DISCUSSION

We show that despite an intensified focus on patient safety since the Institute of Medicine's report *Crossing the Quality Chasm*(17), the population incidence of ADEs is rising with more than 4.3 million persons seeking medical care for an ADE annually. ADE visits were most strongly associated with increasing patient age and polypharmacy; strikingly, the proportion of patients taking five or more medications more than doubled between 1995 and 2005.

The incidence of ADE visits increased with increasing age, peaking at 47.0 ADE visits per 1000 persons among patients 65 years and older. This subset suffered the greatest number of ADEs requiring treatment, with the highest proportion of ADE visits and ADE-related hospital admissions. Both age and number of medications taken by patients were associated with an increased risk of an ADE visit, which is consistent with previous studies implicating age, number of medical problems, and number of medications with the occurrence of ADEs (18–22). Estimates of the proportion of outpatients who experience an ADE and seek medical attention have ranged from 16% to 48% (11,19), indicating that based on an incidence rate of 15.5 ADE visits per 1000 people, up to 10% of the population suffers an outpatient ADE annually (i.e. the incidence rate would be 96.8 visits per 1000 people if instead of 16% of patients, all sought medical care for their ADE). This figure is comparable to rates reported in other studies, although it is difficult to compare results derived from different population groups and patient settings (12,19,22,23). Further study is needed to define the specific circumstances resulting in an ADE—including prescribing errors, medication interactions, and adverse reactions—in order to assess the preventability of events and develop prevention strategies tailored to patients with the highest burden of drug complications. Of note, more than a third of the ADE patient visits were paid for by government-funded sources, highlighting the importance of such strategies in terms of healthcare costs.

A prior study employing NAMCS and NHAMCS data limited to the years 1995 to 2001 and using a different ADE definition, found annual ADE incidences of 10.2 to 15.3 per 1000 population, comparable to our mean annual estimate of 15.5 per 1000 persons (24). Budnitz et al.(13) used a prospective injury surveillance network, the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Network (NEISS-CADES), to examine the frequency of ADE visits in emergency departments over a 2-year period in 2004 and 2005. They found that an estimated 701,547 individuals are treated for ADEs in emergency departments annually, that 16.7% of these require hospitalization, and that ADE-related visits comprise 0.6% of all emergency department visits. These figures are very similar to our results, which show that 791,082 individuals seek emergency department care for ADEs annually, that 14.5% require hospitalization, and that 0.8% of all emergency department visits are attributable to ADEs. The similarity of our results to those from this prospective national study serves to validate the use of the NAMCS and NHAMCS databases for ADE surveillance.

Studies measuring ADEs among hospitalized patients alone capture only a fraction of such events and do not adequately describe the magnitude of this threat to patient safety (1,2,25). In contrast, we examine comprehensive estimates of ADE-related ambulatory visits, including visits to office-based clinics, hospital outpatient clinics, subspecialty clinics, and emergency departments. Furthermore, studies focusing on select populations or specific settings, such as Medicare recipients, primary care clinics, or nursing homes, may not provide a nationally-representative description of ADEs (6,12,19,26). Instead, our study benefited from the use of a multi-year survey that captured a nationally representative sample of patients of all ages treated in outpatient settings throughout the U.S.

An important limitation of the use of NHAMCS for ADE surveillance is the inability to examine what stage of medication use the ADE was related to and ascertain the preventability of the medical complication. NHAMCS also does not permit determination of the outcome of patients suffering an ADE, which would be useful for cost-analysis studies and calculation of ADE fatality rates. The identification of ADEs is clearly subject to under-reporting as well as misclassification. Physicians may not have recognized a patient's symptoms as the result of an ADE or may have failed to include the ADE as a reason for injury or as one of the diagnoses. Alternatively, heightened awareness of ADEs may have affected coding practices and increased the number of events coded as an ADE. However, the increase in ADEs among patients in outpatient clinics was not observed among certain other patient groups—including patients treated in the emergency department and younger patients—making it unlikely that this rise was the result of changes in coding practices. In addition, because there were only approximately 400 ADE-related patient visits surveyed per year, the potential for further analyses based on annual cases is limited. Other limitations of this study are related to the use of survey data, such as the NAMCS and NHAMCS. All data are retrospective and we cannot verify the accuracy or completeness of the data reported. Medications implicated in ADEs are coded at the level of medication groups preventing the study of specific medications implicated in ADEs. There is also missing data, and we were unable to determine the medication causing an ADE in all cases. Finally, errors may occur at the stage of coding and data entry, but the NCHS employs multiple quality control measures and reports low rates of coding errors.

CONCLUSION

We show that both patient age and polypharmacy use are risk factors for an ADE-related healthcare visit. The incidence of ADEs requiring medical treatment has substantially increased between 1995 and 2005, particularly among patients 65 years and older who have an incidence of ADE visits as high as 1 in 20 persons. ADEs in this patient group are also associated with substantial morbidity with a quarter of patients requiring admission. Additional efforts are required to identify preventable ADEs and develop measures to monitor and prevent ADEs in the outpatient population.

Key points

- The population rate of adverse drug events is rising with more than 4.3 million persons seeking medical care for an adverse event annually.
- The highest risk of admission occurs among patients using cardiotonic glycosides, anticoagulants, and anticonvulsants.
- Adverse drug event related visits are significantly associated with polypharmacy use and increasing age.

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Figure 1. National Incidence of Adverse Drug Events Treated in U.S. Outpatient Clinics and Emergency Departments, 1995–2005

A, Mean annual incidence of adverse drug event cases treated in outpatient clinics was 12.7 per 1000 persons (95% CI, 11.5– 14.2); P value for trend <0.001 . Mean annual incidence of adverse drug event cases treated in emergency departments was 2.8 (95% CI, 2.6– 3.1) per 1000 persons; P value for trend $=0.70$. B, Mean annual incidence of adverse drug event cases treated in outpatient clinics and emergency departments was 13.2 per 1000 persons (95% CI, 11.5–14.9) between 1995 and 2000 and 18.1 per 1000 persons (95% CI, 15.6– 20.5) between 2001 and 2005. P value for trend with increasing age was <0.001 during both time periods. Error bars indicate 95% confidence intervals.

Figure 2. National Proportions of Visits to U.S. Outpatient Clinics and Emergency Departments Associated with Three or More Medication Prescriptions, 1995–2005

Mean annual rate of outpatient visits associated with 3 to 4 medication prescriptions was 14.9% (95% CI, 14.6%– 15.2%) and with 5 or more medication prescriptions 9.4% (95% CI, 8.9%–9.8%). *P* value for trend was <0.001 both for use of 3 to 4 medications and use of 5 or more medications.

National Annual Estimates and Demographic Characteristics of Patients with Adverse Drug Events Treated in U.S. Outpatient Clinics and Emergency Departments, 1995–2005

Table 1

Patient Characteristic	Outpatient Clinics (N=1960)		Emergency Departments (N=2409)		Total
	National annual estimate, No. (%)	% of all clinic visits	National annual estimate, No. (%)	% of all ED visits	
Age, y					
0–4	197,176 (5.6)	0.2	55,925 (7.1)	0.5	253,101 (5.8)
5–17	243,659 (6.9)	0.3	65,157 (8.2)	0.4	308,816 (7.1)
18–44	843,947 (23.8)	0.4	315,151 (39.8)	0.7	1,159,098 (26.7)
45–64	1,030,633 (29.1)	0.5	173,323 (21.9)	1.0	1,203,956 (27.8)
≥ 65	1,229,493 (34.7)	0.6	181,525 (23.0)	1.2	1,411,018 (32.5)
Gender					
Female	2,123,264 (59.9)	0.4	512,211 (64.8)	0.9	2,635,475 (60.8)
Male	1,421,645 (40.1)	0.4	278,871 (35.2)	0.6	1,700,516 (39.2)
Race/ethnicity^a					
Non-Hispanic White	2,470,776 (78.5)	0.5	503,979 (71.1)	0.8	2,974,755 (77.1)
Non-Hispanic Black	253,516 (8.0)	0.4	100,593 (14.2)	0.5	354,109 (9.2)
Hispanic	286,833 (9.1)	0.4	68,341 (9.6)	0.7	355,174 (9.2)
Other	137,161 (4.3)	0.4	35,592 (5.0)	0.9	172,753 (4.5)
Number of Medications^b					
1 to 2	2,288,319 (64.6)	0.4	510,835 (64.6)	0.6	2,799,154 (64.6)
3 to 4	688,697 (19.4)	0.6	181,740 (23.0)	1.0	870,438 (20.1)
5 or more	567,892 (16.0)	0.7	98,507 (12.4)	1.5	666,399 (15.4)
Payment source^d					
Private insurance	1,935,597 (57.9)	0.4	365,356 (49.1)	0.8	2,300,953 (56.2)
Government	1,177,485 (35.2)	0.5	267,517 (36.0)	0.8	1,445,002 (35.3)
Self-pay	116,564 (3.5)	0.2	87,390 (11.7)	0.5	203,954 (5.0)
Other	114,118 (3.4)	0.4	23,834 (3.2)	0.7	137,952 (3.4)

Patient Characteristic	Outpatient Clinics (N=1960)		Emergency Departments (N=2409)		Total
	National annual estimate, No. (%)	% of all clinic visits	National annual estimate, No. (%)	% of all ED visits	
Region					
Northeast	863,870 (24.4)	0.5	155,213 (19.6)	0.8	1,019,083 (23.5)
Midwest	877,251 (24.8)	0.5	191,214 (24.2)	0.7	1,068,465 (24.6)
South	1,065,884 (30.1)	0.4	269,148 (34.0)	0.7	1,335,032 (30.8)
West	737,904 (20.8)	0.4	175,507 (22.2)	0.9	913,411 (21.1)
Total	3,544,908 (100)	0.4	791,082 (100)	0.8	4,335,990 (100)

Abbreviations: ED, emergency department

^a Among outpatient clinic cases there were 198 cases with missing race/ethnicity data and 103 cases with missing payment data. Among emergency department cases, 230 and 142 cases were missing race/ethnicity and payment data, respectively.

^b Refers to the number of medications prescribed or continued at the time of the ADE visit.

Table 2

Risk Factors for Adverse Drug Events Treated in U.S. Outpatient Clinics and Emergency Departments, 1995–2005

Risk Factors	Odds Ratio	95% CI
Year of ADE Visit	1.00	0.98–1.02
Age group, y		
0–4	Referent	
5–17	0.92	0.69–1.24
18–44	1.46	1.17–1.82
45–64	1.83	1.45–2.31
≥ 65	2.13	1.63–2.79
Gender		
Female	1.51	1.33–1.70
Male	Referent	
Race/ethnicity^a		
Non-Hispanic White	0.94	0.74–1.19
Non-Hispanic Black	0.69	0.53–0.90
Hispanic	0.87	0.65–1.17
Other	Referent	
Number of Medications^b		
1 to 2	Referent	
3 to 4	1.44	1.24–1.67
5 or more	1.88	1.56–2.24
Payment source^a		
Private insurance	1.11	0.83–1.50
Government	1.00	0.72–1.38
Self-pay	0.77	0.55–1.09
Other	Referent	
Region		
Northeast	0.88	0.72–1.06
Midwest	0.83	0.70–1.00
South	0.87	0.73–1.04
West	Referent	

Abbreviations: CI, confidence interval; ADE adverse drug event

^a Among outpatient clinic cases there were 198 cases with missing race/ethnicity data and 103 cases with missing payment data. Among emergency department cases, 230 and 142 cases were missing race/ethnicity and payment data, respectively.

^b Refers to the number of medications a patient was taking at the time of the ADE visit.

Table 3

National Annual Estimates of Adverse Drug Events Treated in U.S. Outpatient Clinics and Emergency Departments by Medication Class, 1995–2005^a

Medication Class	National Annual Estimate, No. (%)		
	Outpatient Clinic (N=1960)	Emergency Department (N=2409)	Total
Antimicrobial agents	443,836 (12.5)	165,026 (20.9)	608,862 (14.0)
Penicillins	73,062 (2.1)	47,765 (6.0)	120,827 (2.8)
Macrolides	10,677 (0.3)	13,741 (1.7)	24,418 (0.6)
Tetracyclines	37,164 (1.0)	3242 (0.4)	40,406 (0.9)
Cephalosporins	29,072 (0.8)	19,676 (2.5)	48,748 (1.1)
Sulfonamides	64,366 (1.8)	31,696 (4.0)	96,062 (2.2)
Quinolones	30,012 (0.8)	12,935 (1.6)	42,947 (1.0)
Other	208,001 (5.9)	37,410 (4.7)	245,411 (5.7)
Hormones and synthetic substitutes	444,857 (12.6)	49,610 (6.3)	494,467 (11.4)
Adrenal cortical steroids	122,615 (3.5)	11,297 (1.4)	133,912 (3.1)
Estrogen and progesterones	151,234 (4.3)	5637 (0.7)	156,871 (3.6)
Insulin and hypoglycemic agents	74,484 (2.1)	29,410 (3.7)	103,894 (2.4)
Other	96,524 (2.7)	3266 (0.4)	99,790 (2.3)
Cardiovascular agents	404,863 (11.4)	63,445 (8.0)	468,308 (10.9)
Cardiotonic glycosides	17,525 (0.5)	19,964 (2.5)	37,489 (0.9)
Antihyperlipidemics	67,448 (1.9)	8240 (1.0)	75,688 (1.8)
Antihypertensives	202,026 (5.7)	22,700 (2.9)	224,726 (5.2)
Diuretics	35,785 (1.0)	6355 (0.8)	42,140 (1.0)
Other	85,770 (2.4)	6406 (0.8)	92,176 (2.1)
Central Nervous system agents	295,546 (8.3)	105,720 (13.4)	401,266 (9.2)
Anticonvulsants	35,705 (1.0)	22,351 (2.8)	58,056 (1.3)
Anesthetics	9267 (0.3)	9174 (1.2)	18,441 (0.4)
Antidepressants/ mood stabilizers	123,484 (3.5)	19,576 (2.5)	143,060 (3.3)
Antipsychotics	23,516 (0.7)	21,840 (2.8)	45,356 (1.0)
Benzodiazepines	15,136 (0.4)	3607 (0.5)	18,743 (0.5)
Non-benzodiazepine-based sedatives	26,242 (0.7)	12,317 (1.6)	38,559 (0.9)
Stimulants	23,539 (0.7)	7406 (0.9)	30,945 (0.7)
Autonomic agents	25,905 (0.7)	7024 (0.9)	32,929 (0.8)
Other	35,866 (1.0)	10,864 (1.4)	46,730 (1.1)
Analgesics/antipyretics	138,296 (3.9)	89,349 (11.3)	227,645 (5.3)
Opiates	14,355 (0.4)	28,885 (3.7)	43,240 (1.0)
Non-opiate-based agents	123,941 (3.5)	63,423 (8.0)	187,364 (4.3)
Agents affecting primarily skin and mucous membranes	81,437 (2.3)	17,290 (2.2)	98,727 (2.3)

Medication Class	National Annual Estimate, No. (%)		
	Outpatient Clinic (N=1960)	Emergency Department (N=2409)	Total
Antineoplastic and immunosuppressive agents	66,393 (1.9)	16,493 (2.1)	82,886 (1.9)
Antihistamines, cold remedies, and respiratory agents	48,866 (1.4)	20,837 (2.6)	69,703 (1.6)
Hematologic Agents	39,097 (1.1)	21,546 (2.7)	60,643 (1.4)
Topical ear, nose, and throat agents	43,845 (1.2)	6625 (0.8)	50,470 (1.2)
Vaccines	32,141 (0.9)	19,912 (2.5)	52,053 (1.2)
Gastrointestinal agents	30,049 (0.8)	8321 (1.0)	38,370 (0.9)
Agents affecting primarily muscles	9652 (0.3)	4142 (0.5)	13,794 (0.3)
Other agent	113,064 (3.2)	28,645 (3.6)	141,709 (3.3)
Unknown agent	1,387,234 (39.0)	193,631 (24.6)	1,580,865 (36.4)

^a Up to three medications associated with an adverse drug event based on *Supplementary Classification of External Causes of Injury and Poisoning Codes* (E-Codes). There were 96.4% of cases related to a single medication class. ADE cases related to more than one medication class are listed in up to three separate medication classes and percentages may therefore total >100%.

Table 4

National Annual Estimates of Rate of Adverse Drug Events Treated in U.S. Outpatient Clinics and Emergency Departments by Medication Class, 1995–2005

Medication Class	National Annual Estimate, No.		No. of ADE Visits per 1000 Visits Associated with Medication Therapy (95% CI)
	Imputed Total ADE Visits ^{a,b}	Outpatient Visits Associated with Medication Therapy ^c	
Antimicrobial agents	956,652	145,386,473	6.6 (5.4– 8.0)
Penicillins	124,920	43,217,595	2.9 (2.1– 4.0)
Macrolides	24,557	25,354,784	1.0 (0.5– 1.8)
Tetracyclines	40,637	7,483,149	5.4 (2.1– 14.0)
Cephalosporins	49,028	28,364,606	1.7 (1.0– 2.9)
Sulfonamides	96,611	9,892,418	9.8 (6.4– 14.9)
Quinolones	43,195	13,017,106	3.3 (1.8– 6.1)
Hormones and synthetic substitutes	777,600	113,834,618	6.8 (5.3– 8.8)
Adrenal cortical steroids	134,678	29,287,949	4.6 (2.8– 7.4)
Estrogen and progesterones	157,768	35,648,715	4.4 (3.2– 6.2)
Insulin and hypoglycemic agents	104,488	33,261,795	3.1 (1.9– 5.1)
Cardiovascular agents	736,580	153,932,147	4.8 (3.7– 6.2)
Cardiotonic glycosides	37,704	10,462,496	3.6 (2.3– 5.6)
Antihyperlipidemics	76,121	40,718,906	1.9 (1.1– 3.1)
Antihypertensives	226,013	103,595,779	2.2 (1.5– 3.1)
Diuretics		49,606,844	0.8 (0.5– 1.6)
Central Nervous system agents	630,333	261,529,964	2.4 (1.9– 3.0)
Anticonvulsants	58,387	18,394,383	3.2 (2.0– 5.1)
Anesthetics	18,547	11,929,541	1.6 (0.8– 2.9)
Antidepressants/ mood stabilizers	143,880	57,197,767	2.5 (1.8– 3.6)
Antipsychotics	45,615	10,952,088	4.2 (2.4– 7.2)
Sedatives	57,365	41,696,313	1.4 (0.8– 2.5)
Stimulants	31,122	10,012,500	3.1 (1.8– 5.4)
Analgesics/antipyretics	357,751	168,595,966	2.1 (1.6– 2.8)
Opiates	43,485	39,755,748	1.1 (0.8– 1.5)
Non-opiate-based agents	188,437	141,262,606	1.3 (1.0– 1.9)
Agents affecting primarily skin and mucous membranes	155,321	54,191,037	2.9 (1.9– 4.2)
Antineoplastic and immunosuppressive agents	130,312	10,122,617	12.9 (7.8– 21.0)
Antihistamines, cold remedies, and respiratory agents	109,698	115,336,928	1.0 (0.6– 1.6)
Hematologic agents	95,422	29,248,024	3.3 (2.0– 5.4)
Topical ear, nose, and throat	79,400	38,049,667	2.1 (1.3– 3.4)

Medication Class	National Annual Estimate, No.		No. of ADE Visits per 1000 Visits Associated with Medication Therapy (95% CI)
	Imputed Total ADE Visits ^{a,b}	Outpatient Visits Associated with Medication Therapy ^c	
agents			
Vaccines	81,931	33,051,781	2.5 (1.7– 3.6)
Gastrointestinal agents	60,345	61,464,371	1.0 (0.5– 2.1)
Agents affecting primarily muscles	21,698	15,060,353	1.4 (0.8– 2.7)

^a Represents sum of outpatient clinic and emergency department ADE visits.

^b Imputation was performed assuming that the distribution of medication cases was the same among known and unknown cases. The sum of ADE visits for specific medication classes is not necessarily equal to the number of ADE visits for the medication class grouping (indicated in bold), since not all medication classes were included in this table.

^c Includes all visits to outpatient clinics and emergency departments that list medications as part of the patient's outpatient therapy.