SPECIAL ARTICLE

# Emergency Hospitalizations for Adverse Drug Events in Older Americans

Daniel S. Budnitz, M.D., M.P.H., Maribeth C. Lovegrove, M.P.H., Nadine Shehab, Pharm.D., M.P.H., and Chesley L. Richards, M.D., M.P.H.


## ABSTRACT

### BACKGROUND

Adverse drug events are important preventable causes of hospitalization in older adults. However, nationally representative data on adverse drug events that result in hospitalization in this population have been limited.

### METHODS

We used adverse-event data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2007 through 2009) to estimate the frequency and rates of hospitalization after emergency department visits for adverse drug events in older adults and to assess the contribution of specific medications, including those identified as high-risk or potentially inappropriate by national quality measures.

### RESULTS

On the basis of 5077 cases identified in our sample, there were an estimated 99,628 emergency hospitalizations (95% confidence interval [CI], 55,531 to 143,724) for adverse drug events in U.S. adults 65 years of age or older each year from 2007 through 2009. Nearly half of these hospitalizations were among adults 80 years of age or older (48.1%; 95% CI, 44.6 to 51.6). Nearly two thirds of hospitalizations were due to unintentional overdoses (65.7%; 95% CI, 60.1 to 71.3). Four medications or medication classes were implicated alone or in combination in 67.0% (95% CI, 60.0 to 74.1) of hospitalizations: warfarin (33.3%), insulins (13.9%), oral antiplatelet agents (13.3%), and oral hypoglycemic agents (10.7%). High-risk medications were implicated in only 1.2% (95% CI, 0.7 to 1.7) of hospitalizations.

### CONCLUSIONS

Most emergency hospitalizations for recognized adverse drug events in older adults resulted from a few commonly used medications, and relatively few resulted from medications typically designated as high-risk or inappropriate. Improved management of antithrombotic and antidiabetic drugs has the potential to reduce hospitalizations for adverse drug events in older adults.


From the Division of Healthcare Quality Promotion (D.S.B., M.C.L., N.S.), the Office of Prevention through Healthcare (C.L.R.), Centers for Disease Control and Prevention, and the Division of Geriatrics and Gerontology, Emory University School of Medicine (C.L.R.) — all in Atlanta. Address reprint requests to Dr. Budnitz at the Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Rd., NE, Mailstop A-24, Atlanta, GA 30333, or at dbudnitz@cdc.gov.

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Decreasing the number of preventable rehospitalizations by 20% by the end of 2013 is a goal of the $1 billion federal initiative Partnership for Patients, and the pursuit of this goal represents an opportunity to reduce harm to patients and reduce health care costs.[1,2] Adverse drug events are a direct consequence of clinical care and a key focus of the partnership.

Hospitalizations for adverse drug events are likely to increase as Americans live longer, have greater numbers of chronic conditions, and take more medications. Among adults 65 years of age or older, 40% take 5 to 9 medications and 18% take 10 or more.[3] Age-related physiological changes, a greater degree of frailty, a larger number of coexisting conditions, and polypharmacy have been associated with an increased risk of adverse events,[4,5] and older adults are nearly seven times as likely as younger persons to have adverse drug events that require hospitalization.[6]

In a previous study, we found that medications classified as always potentially inappropriate were implicated in only 3.6% of emergency department visits for adverse drug events in older adults, whereas three medications (warfarin, insulin, and digoxin) were implicated in 33.3% of such emergency department visits.[7] Data on the medications that most commonly cause hospitalizations for adverse drug events in the United States have been limited.[8,9] Detailed and drug-specific data are needed to help focus current patient-safety efforts. We used nationally representative public health surveillance data to describe emergency hospitalizations for adverse drug events in persons 65 years of age or older and to assess the contribution of specific medications, including those identified as high-risk or inappropriate by current national health care quality measures.

## Methods

### Data Sources

National estimates of emergency department visits and subsequent hospitalizations for adverse drug events were based on data from the 58 nonpediatric hospitals that participate in the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS–CADES) project, a nationally representative probability sample of hospitals in the United States and its territories with a minimum of six beds and a 24-hour emergency department, which has been described in detail previously.[6,10] In brief, trained coders review the verbatim clinical diagnoses and supporting information in medical records of each emergency department visit to identify adverse drug events diagnosed by treating clinicians. Coders report up to two medications implicated in each adverse event, concomitant medications listed in the medical record, and narrative descriptions of the event. Narrative descriptions of adverse events (physician diagnoses and manifestations) are further coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 9.1. To approximate exposure to specific medications, we used data from the National Ambulatory Medical Care Survey (NAMCS) of office-based clinicians and the National Hospital Ambulatory Medical Care Survey (NHAMCS) of hospital-based outpatient departments and emergency departments.[11]

### Definitions

A surveillance case was defined as hospitalization after an emergency department visit by a person 65 years of age or older during the period from January 1, 2007, through December 31, 2009, for a condition that the treating clinician explicitly attributed to the use of a drug or a drug-specific adverse effect. Drugs included prescription and over-the-counter medications, vaccines, and dietary supplements. Hospitalizations included inpatient admissions, observation admissions (time-limited assessment, treatment, and reassessment, typically lasting <24 to 48 hours), and transfers to another hospital. Adverse events were categorized as allergic reactions (immunologically mediated effects), adverse effects (undesirable pharmacologic or idiosyncratic effects at recommended doses), or unintentional overdoses (excessive doses or supratherapeutic drug effects). Other effects included adverse effects due to medication-delivery methods (e.g., choking) and vaccine reactions. Visits for intentional self-harm, drug abuse, therapeutic failures, and drug withdrawal were excluded.

Outpatient visits for persons 65 years of age or older during which medications were ordered or continued were identified from NAMCS and NHAMCS public-use data files for 2007 and 2008 (the most recent available). Up to eight prescription

or over-the-counter medications, vaccines, and dietary supplements ordered or continued at each visit were recorded.

### OUTCOME MEASURES

The primary outcome measure was hospitalization after an emergency department visit for an adverse event due to medications. Each hospitalization was described with respect to the patient's age and sex, the type of adverse event, implicated medications, and the number of concomitant medications. For hospitalizations in which drugs from a single therapeutic category were implicated, visits were further described by adverse-event manifestations, which were assigned in a mutually exclusive and hierarchical fashion for each therapeutic category.

A secondary outcome measure was hospitalization after an emergency department visit for an adverse event due to a medication currently designated as "high-risk" in the elderly by the 2011 Healthcare Effectiveness Data and Information Set (HEDIS)[12] (see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) or "potentially inappropriate" by the updated Beers criteria for potentially inappropriate medication use in older adults[13] (Table 2 in the Supplementary Appendix). We included such medications regardless of the dose, frequency of use, duration of use, or specific formulation (e.g., short-acting). We did not include Beers-criteria medications classified as potentially inappropriate only when prescribed to patients with certain preexisting conditions, because these have rarely been used in previous studies or in quality measures of drug prescribing.

### STATISTICAL ANALYSIS

Each NEISS–CADES, NAMCS, and NHAMCS case was assigned a sample weight on the basis of inverse probability of selection. For NEISS–CADES cases, the sample weight was adjusted for nonresponse rate and poststratified to adjust for the number of annual hospital emergency department visits; for NAMCS and NHAMCS cases, the sample weight was adjusted for nonresponse and population changes incorporating weight smoothing.[11,14] National estimates of emergency department visits and outpatient medication visits and corresponding 95% confidence intervals were calculated with the use of the SURVEYMEANS procedure in SAS software, version 9.2 (SAS Institute), to account for the sample weights and complex sample designs. To obtain annual estimates, NEISS–CADES estimates for the 3-year period 2007 through 2009 were divided by three, and NAMCS and NHAMCS estimates for the 2-year period 2007 and 2008 were divided by two. Estimates based on small numbers of cases (<20 cases for NEISS–CADES and <30 cases for NAMCS and NHAMCS) and estimates having a coefficient of variation greater than 30% were considered to be statistically unreliable; these estimates are noted in the tables.

To estimate rates of emergency hospitalization for adverse drug events relative to outpatient medication use, we divided the estimated number of hospitalizations for adverse drug events by the estimated number of outpatient visits at which implicated medications were ordered or continued. The 95% confidence interval for each risk estimate incorporated variance estimates for both numerator and denominator components.[15] Because these components were calculated from separate surveillance systems, they were treated as independent (i.e., having zero covariance). Population rates were calculated with the use of "intercensal" estimates (those developed between census years) for 2007 through 2009 from the U.S. Census Bureau.[16]

## RESULTS

On the basis of 12,666 cases, an estimated 265,802 emergency department visits (95% confidence interval [CI], 184,040 to 347,563) for adverse drug events occurred annually from 2007 through 2009 among adults 65 years of age or older. An estimated 37.5% of these visits (99,628 visits; 95% CI, 55,531 to 143,724) required hospitalization, including inpatient admission (34.1%; 95% CI, 27.7 to 40.5), observation admission (2.2%; 95% CI, 1.2 to 3.3), and transfer to another hospital (1.1%; 95% CI, 0.5 to 1.7).

Nearly half of hospitalizations for adverse drug events (48.1%; 95% CI, 44.6 to 51.6) involved adults 80 years of age or older (Table 1). The population rate of hospitalizations for adverse drug events was 3.5 times as high among adults 85 years of age or older as among adults 65 to 69 years of age (4.6 hospitalizations per 1000 persons [95% CI, 2.5 to 6.8] vs. 1.3 [95% CI, 0.7 to 1.8]) and remained significantly elevated when stratified according to number of concomitant medications (0 to 4 or ≥5 concomitant medications). Women accounted

**Table 1. Number of Cases and National Estimates of Emergency Department Visits and Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, According to Patient and Case Characteristics, 2007–2009.***

| Characteristic | Hospitalizations | | | Emergency Department Visits Not Resulting in Hospitalization | | |
|---|---|---|---|---|---|---|
| | No. of Cases (N=5077) | Annual National Estimate (N=99,628) | | No. of Cases (N=7,589) | Annual National Estimate (N=166,174) | |
| | | *no.* | *% (95% CI)* | | *no.* | *% (95% CI)* |
| Age | | | | | | |
| 65–69 yr | 801 | 14,179 | 14.2 (12.0–16.5) | 1669 | 36,380 | 21.9 (19.7–24.1) |
| 70–74 yr | 924 | 18,257 | 18.3 (16.6–20.1) | 1546 | 32,575 | 19.6 (18.4–20.8) |
| 75–79 yr | 1001 | 19,248 | 19.3 (18.2–20.5) | 1628 | 35,702 | 21.5 (20.1–22.9) |
| 80–84 yr | 1110 | 22,619 | 22.7 (20.9–24.5) | 1366 | 31,266 | 18.8 (17.2–20.4) |
| ≥85 yr | 1241 | 25,326 | 25.4 (23.0–27.9) | 1380 | 30,251 | 18.2 (16.6–19.8) |
| Sex† | | | | | | |
| Female | 2969 | 59,278 | 59.5 (57.4–61.6) | 4511 | 99,495 | 59.9 (57.7–62.0) |
| Male | 2106 | 40,302 | 40.5 (38.4–42.5) | 3076 | 66,604 | 40.1 (37.9–42.3) |
| Type of adverse event | | | | | | |
| Unintentional overdose | 3375 | 65,450 | 65.7 (60.1–71.3) | 3608 | 75,982 | 45.7 (40.7–50.7) |
| Adverse effect | 1390 | 27,613 | 27.7 (22.3–33.1) | 2313 | 50,240 | 30.2 (26.0–34.4) |
| Allergic reaction | 267 | 5,617 | 5.6 (3.4–7.9) | 1388 | 33,838 | 20.4 (17.0–23.7) |
| Other‡ | 45 | 948 | 1.0 (0.7–1.2) | 280 | 6,115 | 3.7 (2.9–4.4) |
| No. of implicated medications | | | | | | |
| 1 | 4204 | 82,050 | 82.4 (78.5–86.3) | 6471 | 141,939 | 85.4 (82.5–88.3) |
| 2 | 873 | 17,578 | 17.6 (13.7–21.5) | 1118 | 24,235 | 14.6 (11.7–17.5) |
| No. of concomitant medications | | | | | | |
| None documented | 773 | 18,324 | 18.4 (12.0–24.8) | 2103 | 56,082 | 33.7 (22.8–44.7) |
| 1–4 | 1459 | 26,731 | 26.8 (21.9–31.8) | 2156 | 43,819 | 26.4 (21.2–31.5) |
| 5–9 | 2115 | 40,443 | 40.6 (35.0–46.2) | 2554 | 50,420 | 30.3 (24.0–36.7) |
| ≥10 | 730 | 14,130 | 14.2 (9.2–19.1) | 776 | 15,853 | 9.5 (6.8–12.3) |

* Estimates were based on data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS–CADES) project. Hospitalizations included inpatient admissions, observation admissions (time-limited assessment, treatment, and reassessment, typically lasting <24 to 48 hours), and transfers to another hospital. Patients who were not hospitalized included those who were treated and released or left against medical advice, and one patient for whom the disposition was not documented. Because each case was individually weighted, categories with the same numbers of cases may not reflect identical national estimates.

† Data were not available for two hospitalizations and two emergency department visits that did not result in hospitalization.

‡ Other adverse events included vaccination reactions and adverse events due to medication-delivery methods (e.g., choking and injection-site reactions).

for three fifths of hospitalizations (59.5%), but the population rate was not significantly higher for women (2.7 hospitalizations per 1000 women [95% CI, 1.5 to 3.8] vs. 2.5 per 1000 men [95% CI, 1.3 to 3.6]). Emergency department visits that resulted in hospitalization, as compared with visits that did not result in hospitalization, were more likely to involve unintentional overdoses (65.7% vs. 45.7%) and five or more concomitant medications (54.8% vs. 39.9%).

**Table 2. National Estimates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, According to Therapeutic Category, 2007–2009.***

| Therapeutic Category | Annual National Estimate of Hospitalizations (N=99,628) | | Proportion of Emergency Department Visits Resulting in Hospitalization |
|---|---|---|---|
| | *no.* | *% (95% CI)* | % |
| Hematologic agents | 42,104 | 42.3 (35.5–49.0) | 44.6 |
| Endocrine agents | 22,726 | 22.8 (16.7–28.9) | 42.1 |
| Cardiovascular agents | 9,800 | 9.8 (7.1–12.5) | 42.3 |
| Central nervous system agents | 9,621 | 9.7 (7.6–11.8) | 32.2 |
| Antiinfective agents | 3,759 | 3.8 (2.6–4.9) | 17.4 |
| Antineoplastic agents | 2,882† | 2.9 (0.9–4.9)† | 51.0 |
| Other agents | 3,211 | 3.2 (2.6–3.8) | 15.0 |
| Medications not stated or not known | 957 | 1.0 (0.5–1.5) | 20.6 |
| Medications in more than one therapeutic category | 4,568† | 4.6 (2.7–6.5) | 41.2 |

* Estimates were based on data from the NEISS–CADES project. The proportion of emergency department visits resulting in hospitalization is the ratio of hospitalizations to total emergency department visits for adverse drug events involving the specified therapeutic category.
† The coefficient of variation was greater than 30%.

Hematologic agents, endocrine agents, cardiovascular agents, central nervous system agents, and antiinfective agents were the five most common therapeutic categories implicated, accounting for an estimated 88.3% (95% CI, 84.7 to 91.9) of hospitalizations for adverse drug events (Table 2). Antineoplastic agents and the three most commonly implicated therapeutic categories accounted for the highest proportion of emergency department visits resulting in hospitalization.

Within therapeutic categories, the proportion of emergency department visits resulting in hospitalization varied according to the manifestations of adverse drug events (Table 3). Most hospitalizations attributed to hematologic agents were for acute hemorrhages (71.3%). More than 70% of emergency department visits for intracranial hemorrhages, gastrointestinal hemorrhages, and hemoptysis attributed to hematologic agents resulted in hospitalization. An estimated 21,010 hospitalizations (95% CI, 10,126 to 31,894) were for warfarin-related hemorrhages, representing 63.3% (95% CI, 56.9 to 69.8) of all warfarin-related hospitalizations. An estimated 88.1% (95% CI, 78.7 to 97.5) of antiplatelet-related hospitalizations were for hemorrhages. Nearly all hospitalizations attributed to endocrine agents were for hypoglycemia (94.6%). An estimated two thirds of these hospitalizations (66.6%; 95% CI, 56.9 to 76.3) involved neurologic symptoms (loss of consciousness, seizures, changes in mental status, or other neurologic sequelae). Of hospitalizations attributed to cardiovascular agents, an estimated one third were for electrolyte or fluid-volume disturbances or nonspecific weakness (33.2%), with 68.9% of emergency department visits for these manifestations resulting in hospitalization.

Thirteen medications and medication classes were implicated, alone or in combination, in at least 1% of estimated hospitalizations for adverse drug events (Table 4). The four most commonly implicated — warfarin (33.3%), insulins (13.9%), oral antiplatelet agents (13.3%), and oral hypoglycemic agents (10.7%) — accounted for an estimated two thirds of hospitalizations (67.0%; 95% CI, 60.0 to 74.1), and these remained the most commonly implicated drugs when stratified according to age (65 to 74 years, 75 to 84 years, and ≥85 years) and sex. Nearly all hospitalizations involving warfarin (95.1%; 95% CI, 91.7 to 98.4), insulins (99.4%; 95% CI, 98.7 to 100.0), or oral hypoglycemic agents (99.1%; 95% CI, 98.1 to 100.0) resulted from unintentional overdoses. Of hospitalizations attributed to warfarin, another medication was implicated in 12.5% of visits (95% CI, 6.7 to 18.3), most often an oral antiplatelet agent (6.7%; 95% CI, 3.2 to 10.2). Of hospitalizations attributed to insulins, another medication was impli-

**Table 3. National Estimates of Emergency Hospitalizations for Common Manifestations of Adverse Drug Events in Older U.S. Adults, 2007–2009.***

| Therapeutic Category and Adverse-Event Manifestation† | Annual National Estimate of Hospitalizations | Proportion of Emergency Department Visits Resulting in Hospitalization |
|---|---|---|
| | % *(95% CI)* | % |
| **Hematologic agents** | | |
| Intracranial hemorrhage | 5.6 (2.1–9.1)‡ | 99.7 |
| Hemoptysis | 2.0 (1.1–2.8) | 73.6 |
| Gastrointestinal hemorrhage | 40.8 (29.9–51.7) | 84.7 |
| Genitourinary hemorrhage | 4.7 (3.2–6.2) | 42.4 |
| Epistaxis | 6.1 (4.3–8.0) | 10.6 |
| Skin or wound hemorrhage | 6.8 (4.5–9.1) | 24.5 |
| Other type of hemorrhage | 5.3 (2.7–8.0) | 27.5 |
| Elevated INR, abnormal laboratory values, or drug toxicity not otherwise described | 23.7 (16.8–30.6) | 59.5 |
| **Endocrine agents** | | |
| Hypoglycemia with loss of consciousness or seizure | 26.0 (13.5–38.4) | 57.5 |
| Hypoglycemia with altered mental status or other neurologic sequelae | 40.7 (31.8–49.5) | 42.4 |
| Hypoglycemia with cardiovascular sequelae | 8.3 (6.1–10.4) | 49.6 |
| Hypoglycemia with weakness, dyspnea, or respiratory distress | 5.7 (3.0–8.5) | 47.5 |
| Hypoglycemia with other or unspecified sequelae | 14.0 (6.2–21.8) | 37.3 |
| **Cardiovascular agents** | | |
| Electrolyte or fluid-volume disturbance, weakness, or lethargy | 33.2 (25.7–40.8) | 68.9 |
| Cardiac arrhythmia or abnormality in heart rate or blood pressure | 17.9 (10.9–24.9) | 47.3 |
| Altered mental status or neuropsychiatric or other neurologic effect | 8.8 (5.3–12.4) | 45.5 |
| Dizziness, syncope, or fall or other injury | 9.9 (5.4–14.5) | 39.6 |
| Allergic reaction | 16.1 (7.5–24.7) | 24.1 |
| **Central nervous system agents** | | |
| Fall or other injury | 14.9 (9.1–20.8) | 36.4 |
| Altered mental status | 42.2 (37.7–46.7) | 52.1 |
| Neuropsychiatric or other neurologic effect | 9.7 (5.2–14.2) | 27.7 |
| Dizziness, syncope, weakness, dyspnea, or respiratory distress | 12.1 (7.8–16.4) | 23.0 |
| Gastrointestinal effect | 9.9 (4.9–14.9) | 23.9 |
| **Antiinfective agents** | | |
| Neurologic effect | 18.3 (11.8–24.7) | 20.0 |
| Dyspnea, weakness, or abnormality in heart rate or blood pressure | 22.5 (15.8–29.2) | 32.5 |
| Gastrointestinal effect | 20.5 (10.6–30.4) | 22.7 |
| Allergic reaction | 36.2 (26.8–45.5) | 12.0 |

* Estimates were based on data from the NEISS–CADES project. Only the most common manifestations associated with adverse events are listed for the five most frequently implicated therapeutic categories. The proportion of emergency department visits resulting in hospitalization is the ratio of hospitalizations to total emergency department visits for adverse drug events involving the specified therapeutic category and manifestation. Estimates based on fewer than 20 cases are not shown. INR denotes international normalized ratio.

† Adverse-event manifestations are mutually exclusive and are listed hierarchically and in descending order of general severity within each therapeutic category (top to bottom).

‡ The coefficient of variation was greater than 30%.

**Table 4. National Estimates of Medications Commonly Implicated in Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.***

| Medication | Annual National Estimate of Hospitalizations (N=99,628) | | Proportion of Emergency Department Visits Resulting in Hospitalization |
|---|---|---|---|
| | *no.* | *% (95% CI)* | % |
| Most commonly implicated medications† | | | |
| Warfarin | 33,171 | 33.3 (28.0–38.5) | 46.2 |
| Insulins | 13,854 | 13.9 (9.8–18.0) | 40.6 |
| Oral antiplatelet agents | 13,263‡ | 13.3 (7.5–19.1) | 41.5 |
| Oral hypoglycemic agents | 10,656 | 10.7 (8.1–13.3) | 51.8 |
| Opioid analgesics | 4,778 | 4.8 (3.5–6.1) | 32.4 |
| Antibiotics | 4,205 | 4.2 (2.9–5.5) | 18.3 |
| Digoxin | 3,465 | 3.5 (1.9–5.0) | 80.5 |
| Antineoplastic agents | 3,329‡ | 3.3 (0.9–5.8)‡ | 51.5 |
| Antiadrenergic agents | 2,899 | 2.9 (2.1–3.7) | 35.7 |
| Renin–angiotensin inhibitors | 2,870 | 2.9 (1.7–4.1) | 32.6 |
| Sedative or hypnotic agents | 2,469 | 2.5 (1.6–3.3) | 35.2 |
| Anticonvulsants | 1,653 | 1.7 (0.9–2.4) | 40.0 |
| Diuretics | 1,071‡ | 1.1 (0.4–1.8)‡ | 42.4 |
| High-risk or potentially inappropriate medications§ | | | |
| HEDIS high-risk medications | 1,207 | 1.2 (0.7–1.7) | 20.7 |
| Beers-criteria potentially inappropriate medications | 6,607 | 6.6 (4.4–8.9) | 42.0 |
| Beers-criteria potentially inappropriate medications, excluding digoxin | 3,170 | 3.2 (2.3–4.1) | 27.6 |

* Estimates were based on data from the NEISS–CADES project. The proportion of emergency department visits resulting in hospitalization is the ratio of hospitalizations to total emergency department visits for adverse drug events involving the specified medication or medication class.

† The medications listed were implicated in at least 1% of estimated emergency hospitalizations. Oral antiplatelet agents were defined as aspirin, aspirin–dipyridamole, cilostazol, clopidogrel, dipyridamole, prasugrel, and ticlopidine. Antiadrenergic agents were defined as beta-blockers, calcium-channel blockers, and centrally and peripherally acting alpha-adrenergic blockers. Sedative or hypnotic agents were defined as benzodiazepines, barbiturates, and nonbenzodiazepine or non–barbituric acid derivatives.

‡ The coefficient of variation was greater than 30%.

§ High-risk medications are those designated as such in the elderly by the 2011 Healthcare Effectiveness Data and Information Set (HEDIS).[12] Potentially inappropriate medications are those identified by the updated 2002 Beers criteria for potentially inappropriate medication use in older adults. All high-risk or potentially inappropriate medications were included in the analysis, regardless of dose, frequency of use, formulation (e.g., short-acting), or duration of use.

cated in 15.4% of visits (95% CI, 7.9 to 22.9), most often an oral hypoglycemic agent (10.1%; 95% CI, 6.3 to 14.0).

An estimated 1.2% of hospitalizations for adverse drug events were attributed to HEDIS high-risk medications and 6.6% were attributed to Beers-criteria potentially inappropriate medications. However, more than half of the hospitalizations for Beers-criteria medications involved digoxin, which is considered allowable if used in daily doses of 0.125 mg or less or if used to treat atrial arrhythmias. When digoxin was excluded, at least one of the remaining Beers-criteria medications was implicated in 3.2% of hospitalizations; a non-Beers criteria medication was also implicated in more than half of these hospitalizations (52.8%; 95% CI, 45.3 to 60.3).

When the estimated number of outpatient visits during which medications were ordered or continued was taken into account, the rates of warfarin-related hospitalizations (20.0 hospitalizations per 10,000 medication visits [95% CI, 9.4 to 30.6]) and insulin-related hospitalizations (19.1 hospitalizations per 10,000 medication visits [95% CI, 8.0 to

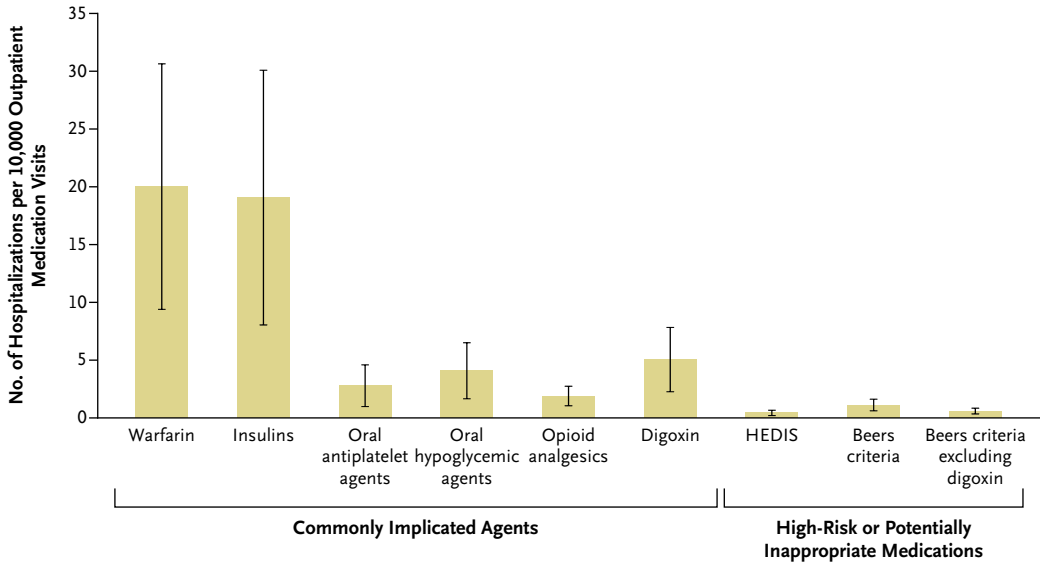


**Figure 1. Estimated Rates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.**

Estimates were based on hospitalization data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project for 2007 through 2009, and data for outpatient visits during which medications were ordered or continued are from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey for 2007 and 2008. High-risk medications are those designated as such in the elderly by the 2011 Healthcare Effectiveness Data and Information Set (HEDIS).[12] Potentially inappropriate medications are those identified by the updated 2002 Beers criteria for potentially inappropriate medication use in older adults.[13] All high-risk or potentially inappropriate medications were included in the analysis, regardless of the dose, frequency of use, formulation (e.g., short-acting), or duration of use. I bars denote 95% confidence intervals. For oral antiplatelet agents, the coefficient of variation was greater than 30%.

30.1]) were at least 48 times as high as the hospitalization rates for adverse drug events due to HEDIS high-risk medications (0.4 hospitalizations per 10,000 medication visits [95% CI, 0.2 to 0.7]) and at least 17 times as high as the hospitalization rates for Beers-criteria potentially inappropriate medications (1.1 hospitalizations per 10,000 medication visits [95% CI, 0.6 to 1.6]) (Fig. 1). Of the commonly implicated medications, digoxin had the third highest hospitalization rate for adverse drug events (5.0 hospitalizations per 10,000 medication visits [95% CI, 2.3 to 7.8]). When digoxin was excluded, the rate for Beers-criteria medications was nearly halved (0.6 hospitalizations per 10,000 medication visits [95% CI, 0.3 to 0.8]).

## DISCUSSION

This study provides detailed national estimates and rates of emergency hospitalizations for adverse drug events in older adults in the United States. An estimated 99,628 emergency hospitalizations for adverse drug events occur each year among older adults, most of which are for supratherapeutic effects. Warfarin was implicated in about one third of these hospitalizations; insulins, oral antiplatelet agents, and oral hypoglycemic agents accounted for about another third. Medications commonly designated as high-risk or potentially inappropriate by current national quality measures were rarely implicated. Coordinated efforts to promote the safe management of antithrombotic and antidiabetic agents have the potential to substantially reduce harm to patients.

Timely, population-representative data on adverse drug events are important as treatment practices evolve and new safety initiatives are introduced, but nearly all published studies of hospitalizations for adverse drug events in the past 15 years have been conducted outside the United States.[8,9,17] Three single-center U.S. studies conducted in the late 1990s used computer-based screening with physician review,[18] the hospital's voluntary system for reporting adverse drug re-

actions,[19] and retrospective pharmacist review[20] to identify hospitalizations related to adverse drug events. Despite these methodologic differences, anticoagulants were commonly implicated in all three studies, and antidiabetic agents were commonly implicated in two studies. One study estimated that 1.4% of admissions were for adverse drug events.[18] Similarly, on the basis of an estimated 6.7 million emergency hospitalizations annually,[21] our findings suggest that adverse drug events result in an estimated 1.5% of emergency hospitalizations among older adults (1 of every 67 emergency hospitalizations).

Despite a narrow definition of adverse drug events, nearly 100,000 emergency hospitalizations for such events occur annually, representing a substantial burden. The number is more than the estimated number of emergency admissions for delirium or dementia (75,000) and is similar to the numbers of emergency admissions for biliary tract disease (110,000) and for skin or subcutaneous-tissue infections (118,000) among older adults.[22] In addition, the finding that more than 66,000 emergency hospitalizations were for adverse effects of a few, commonly prescribed antithrombotic and antidiabetic agents has important implications for efforts to reduce harm to patients and to reduce health care costs.[23] With an estimated 21,010 hospitalizations for warfarin-related hemorrhages, the cost for this one type of adverse drug event is probably hundreds of millions of dollars annually.[24]

Although there may be some correlation between health care expenditures and inappropriate medication use,[25] evidence linking inappropriate prescribing to adverse outcomes is mixed and contradictory,[26,27] and we found that rates of hospitalization for adverse drug events were considerably lower for these drugs than for warfarin and insulins. Novel oral anticoagulants may be an alternative to warfarin,[28] but until the role of these agents is better defined, and as long as warfarin remains the most common cause of emergency hospitalizations for adverse drug events, safety policies should address these harms. Some assume that efforts to minimize the risk of adverse events come at the expense of reductions in the benefits of therapy. The risks from some drugs may be mitigated only by eliminating or restricting their use, but in the case of warfarin, anticoagulation-management services have been shown to improve anticoagulation control and reduce both thromboembolic and bleeding events.[29,30]

Although oral antiplatelet agents are not as amenable to dose adjustment and monitoring as warfarin is, the substantial contribution that they make to hospitalizations in older adults is a reminder of the need for careful consideration of risks and benefits for individual patients and counseling about early recognition of hemorrhagic symptoms in this patient population.[31,32] The high numbers of hospitalizations for hypoglycemia from antidiabetic agents is consistent with mounting evidence of adverse outcomes from hypoglycemia and suggestions that current guideline and performance measures may not reflect optimal diabetes management for all patients.[33] Implementing quality measures to monitor safe use of medications for chronic conditions can be more challenging than implementing measures that simply identify the use of potentially inappropriate medications that often have therapeutic alternatives,[34,35] but safety measures for monitoring warfarin, anticonvulsants, and digoxin (medications with high hospitalization rates) have been endorsed by the National Quality Forum, and implementation of these measures may be the starting point for wider adoption of measures that address common causes of hospitalization for adverse drug events.[36]

Public health surveillance systems can provide timely, representative information that can be used to assess progress in prevention efforts. However, these data also have limitations. First, we probably underestimated the number of emergency hospitalizations because NEISS–CADES relies on identification and documentation of adverse drug events by emergency department physicians, which may introduce a bias toward the detection of acute, known drug effects or effects for which emergency department testing is available.[6,37] Thus, adverse drug events that are typically confirmed in the course of hospitalization (e.g., gastrointestinal bleeding attributed to nonsteroidal antiinflammatory drugs) or identified by patient interview, comprehensive chart review, or modeling of long-term outcomes are less likely to be captured. Second, our estimates of emergency hospitalizations for adverse drug events do not include patients who were directly admitted for diagnostic evaluation or transferred from another hospital without undergoing an initial evaluation in the emer-

gency department. Third, although NAMCS and NHAMCS data are commonly used to estimate outpatient medication use,[38-40] they do not provide direct estimates of person-year exposure to medications. In addition, these data exclude medications initiated in nursing homes, in ambulatory-surgery centers, at hospital discharge, and through telephone or e-mail contact.[11] The rates of hospitalization per outpatient medication visit should be viewed as approximations of person-year exposure to various medications.

Our findings suggest that efforts to improve medication safety for older adults should focus on areas in which improvements are most likely to have sizable, clinically significant, and measurable effects, such as improving the management of antithrombotic and antidiabetic drugs.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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## REFERENCES

1. Kocher R, Emanuel EJ, DeParle NA. The Affordable Care Act and the future of clinical medicine: the opportunities and challenges. Ann Intern Med 2010;153:536-9.
2. HealthCare.gov. Partnership for patients: better care, lower costs. Washington, DC: Department of Health and Human Services (http://www.healthcare.gov/center/programs/partnership/index.html).
3. Patterns of medication use in the United States, 2006: a report from the Slone Survey. Boston: Slone Epidemiology Center at Boston University (http://www.bu.edu/slone/SloneSurvey/AnnualRpt/SloneSurveyWebReport2006.pdf).
4. ElDesoky ES. Pharmacokinetic-pharmacodynamic crisis in the elderly. Am J Ther 2007;14:488-98.
5. McLean AJ, Le Couteur DG. Aging, biology, and geriatric clinical pharmacology. Pharmacol Rev 2004;56:163-84.
6. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA 2006;296:1858-66.
7. Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. Ann Intern Med 2007;147:755-65.
8. Howard RL, Avery AJ, Slavenburg S, et al. Which drugs cause preventable admissions to hospital? A systematic review. Br J Clin Pharmacol 2007;63:136-47.
9. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 2008;168:1890-6.
10. Jhung MA, Budnitz DS, Mendelsohn AB, Weidenbach KN, Nelson TD, Pollock DA. Evaluation and overview of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project (NEISS-CADES). Med Care 2007;45:Suppl 2:S96-S102.
11. Ambulatory health care data. Atlanta: Centers for Disease Control and Prevention (http://www.cdc.gov/nchs/ahcd.htm).
12. Healthcare Effectiveness Data and Information Set (HEDIS). 2011 Final NDC lists: use of high-risk medications in the elderly (DAE). Washington, DC: National Committee on Quality Assurance (http://www.ncqa.org/tabid/1274/Default.aspx).
13. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med 2003;163:2716-24. [Erratum, Arch Intern Med 2004;164:298.]
14. National Electronic Injury Surveillance System All Injury Program: sample design and implementation. Washington, DC: Consumer Product Safety Commission, 2002.
15. Kish L. Survey sampling. New York: Wiley Interscience, 1995.
16. Bridged-race population estimates, United States: July 1st resident population by state, county, age, sex, bridged-race, and Hispanic origin, compiled from 1990-1999 bridged-race intercensal population estimates and 2000-2009 (Vintage 2009) bridged-race postcensal population estimates, on CDC WONDER on-line database. Atlanta: Centers for Disease Control and Prevention (http://wonder.cdc.gov/bridged-race-v2009.html).
17. Onder G, Pedone C, Landi F, et al. Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA). J Am Geriatr Soc 2002;50:1962-8.
18. Jha AK, Kuperman GJ, Rittenberg E, Teich JM, Bates DW. Identifying hospital admissions due to adverse drug events using a computer-based monitor. Pharmacoepidemiol Drug Saf 2001;10:113-9.
19. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 2002;36:1331-6.
20. Wu WK, Pantaleo N. Evaluation of outpatient adverse drug reactions leading to hospitalization. Am J Health Syst Pharm 2003;60:253-9.
21. Buie VC, Owings MF, DeFrances CJ, Golosinskiy A. National Hospital Discharge Survey: 2006 summary. Vital Health Stat 2010;13:168.
22. HCUPnet: Healthcare Cost and Utilization Project. Rockville, MD: Agency for Healthcare Research and Quality (http://hcupnet.ahrq.gov).
23. Wachter RM. Patient safety at ten: unmistakable progress, troubling gaps. Health Aff (Millwood) 2010;29:165-73.
24. Kim MM, Metlay J, Cohen A, et al. Hospitalization costs associated with warfarin-related bleeding events among older community-dwelling adults. Pharmacoepidemiol Drug Saf 2010;19:731-6.
25. Zhang Y, Baicker K, Newhouse JP. Geographic variation in the quality of prescribing. N Engl J Med 2010;363:1985-8.
26. Curtiss FR, Fairman KA. Protecting patients from adverse drug events: propoxyphene, PIMs, and drugs to avoid in older adults. J Manag Care Pharm 2011;17:60-9.
27. Page RL II, Ruscin JM. The risk of adverse drug events and hospital-related morbidity and mortality among older adults with potentially inappropriate medication use. Am J Geriatr Pharmacother 2006;4:297-305.
28. Gage BF. Can we rely on RE-LY? N Engl J Med 2009;361:1200-2.
29. Streiff MB, Kraus PS, Pronovost P. Penny-wise, pound-foolish? Highmark Medicare Services' proposal for anticoagulation clinic reimbursement. Ann Pharmacother 2010;44:733-6.
30. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists. Chest 2008;133:Suppl:160S-198S.
31. Spinler SA. Safety and tolerability of antiplatelet therapies for the secondary

prevention of atherothrombotic disease. Pharmacotherapy 2009;29:812-21.
**32.** Shehab N, Sperling LS, Kegler SR, Budnitz DS. National estimates of emergency department visits for hemorrhage-related adverse events from clopidogrel plus aspirin and from warfarin. Arch Intern Med 2010;170:1926-33.
**33.** Pogach L, Aron D. Balancing hypoglycemia and glycemic control: a public health approach for insulin safety. JAMA 2010;303:2076-7.
**34.** Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet 2007;370:173-84.
**35.** Steinman MA, Handler SM, Gurwitz JH, Schiff GD, Covinsky KE. Beyond the prescription: medication monitoring and adverse drug events in older adults. J Am Geriatr Soc 2011;59:1513-20.
**36.** NQF-endorsed standards. Washington, DC: National Quality Forum (http://www.qualityforum.org/Measures_List.aspx).
**37.** Wears RL, Nelson LS. Believing is seeing. Ann Emerg Med 2010;55:511-2.
**38.** Grijalva CG, Nuorti JP, Griffin MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. JAMA 2009;302:758-66.
**39.** Goulding MR. Inappropriate medication prescribing for elderly ambulatory care patients. Arch Intern Med 2004;164:305-12.
**40.** Burt CW. National trends in use of medications in office-based practice, 1985-1999. Health Aff (Millwood) 2002;21:206-14.