

Medication Use Leading to Emergency Department Visits for Adverse Drug Events in Older Adults

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Background: The Beers criteria identify inappropriate use of medications in older adults. The number of and risk for adverse events from these medications are unknown.

Objective: To estimate the number of and risk for emergency department visits for adverse events involving Beers criteria medications compared with other medications.

Design: Nationally representative, public health surveillance of adverse drug events and a cross-sectional survey of outpatient medical visits.

Setting: National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance System, 2004–2005; National Ambulatory Medical Care Survey, 2004; and National Hospital Ambulatory Medical Care Survey, 2004.

Participants: Persons 65 years of age or older seeking emergency department and outpatient care.

Measurements: Estimated number of and risks for emergency department visits for adverse drug events involving Beers criteria medications and other medications.

Results: Among U.S. patients 65 years of age or older, an estimated 177 504 emergency department visits (95% CI, 100 155 to

254 854 visits) for adverse drug events occurred both years. An estimated 3.6% (CI, 2.8% to 4.5%) of these visits were for adverse events medications considered to be always potentially inappropriate, according to the Beers criteria, and 33.3% (CI, 27.8% to 38.7%) of visits were for adverse events from 3 other medications (warfarin [17.3%], insulin [13.0%], and digoxin [3.2%]). Accounting for outpatient prescription frequency, the risk for emergency department visits for adverse events due to these 3 medications was 35 times (CI, 9.6 to 61) greater than that for medications considered to be always potentially inappropriate.

Limitation: Adverse events were identified only in emergency departments.

Conclusion: Compared with other medications, Beers criteria medications caused low numbers of and few risks for emergency department visits for adverse events. Performance measures and interventions targeting warfarin, insulin, and digoxin use could prevent more emergency department visits for adverse events.

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Adverse drug events cause clinically significant morbidity and mortality and are associated with large economic costs (1–5). They are common in older adults, regardless of whether they live in the community, reside in long-term care facilities, or are hospitalized (5–9). Most physicians recognize that prescribing medications to older patients requires special considerations, but nongeriatricians are typically unfamiliar with the most commonly used measure of medication appropriateness for older patients: the Beers criteria (10–12).

The Beers criteria are a consensus-based list of medications identified as potentially inappropriate for use in older adults. The criteria were introduced in 1991 to help researchers evaluate prescription quality in nursing homes (10). The Beers criteria were updated in 1997 and 2003 to apply to all persons age 65 years or older, to include new medications judged to be ineffective or to pose unnecessarily high risk, and to rate the severity of adverse outcomes (11, 12). Prescription rates of Beers criteria medications have become a widely used measure of quality of care for older adults in research studies in the United States and elsewhere (13–26).

The application of the Beers criteria as a measure of health care quality and safety has expanded beyond research studies. The Centers for Medicare & Medicaid Services incorporated the Beers criteria into federal safety regulations for long-term care facilities in 1999 (27). The

prescription rate of potentially inappropriate medications is one of the few medication safety measures in the National Healthcare Quality Report (28) and has been introduced as a Health Plan and Employer Data and Information Set quality measure for managed care plans (29).

Despite widespread adoption of the Beers criteria to measure prescription quality and safety, as well as proposals to apply these measures to additional settings, such as medication therapy management services under Medicare Part D (30), population-based data on the effect of adverse events from potentially inappropriate medications are sparse and do not compare the risks for adverse events from Beers criteria medications against those from other medications (31, 32).

Adverse drug events that lead to emergency department visits are clinically significant adverse events (5) and

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Context

Emergency department visits by older adults are often due to adverse drug events, but the proportion of these visits that are the result of drugs designated as inappropriate for use in this population is unknown.

Contribution

Analyses of a national surveillance study of adverse drug events and a national outpatient survey estimate that Americans age 65 years or older have more than 175 000 emergency department visits for adverse drug events yearly. Three commonly prescribed drugs accounted for more than one third of visits: warfarin, insulin, and digoxin.

Caution

The study was limited to adverse events in the emergency department.

Implication

Strategies to decrease adverse drug events among older adults should focus on warfarin, insulin, and digoxin.

—The Editors

result in increased health care resource utilization and expense (6). We used nationally representative public health surveillance data to estimate the number of emergency de-

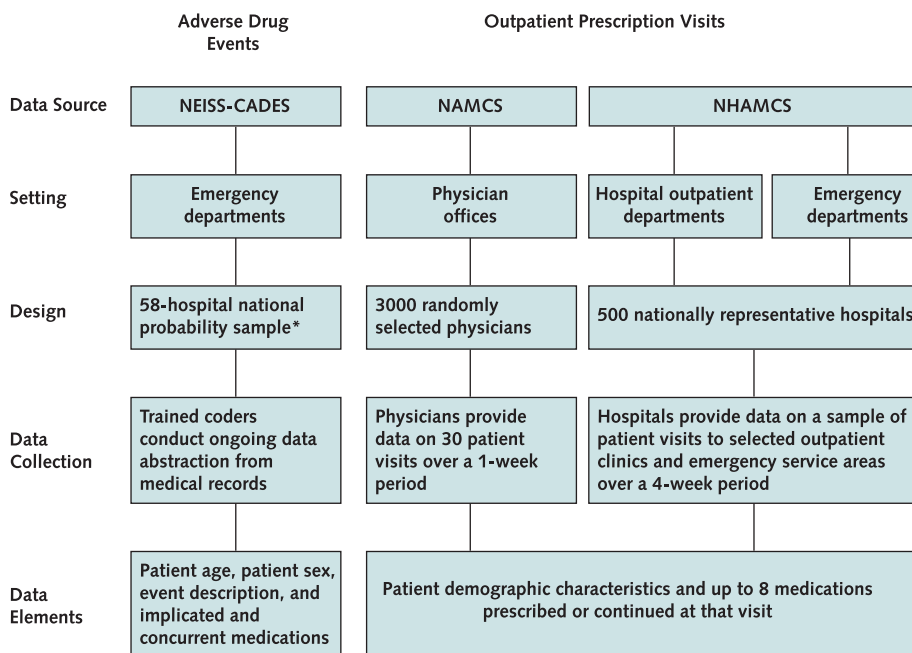
partment visits for adverse drug events involving Beers criteria medications and compared the number with that for adverse drug events involving other medications. We also estimated the frequency of outpatient prescription of Beers criteria medications and other medications to calculate and compare the risks for emergency department visits for adverse drug events per outpatient prescription visit.

METHODS

Data Sources

National estimates of emergency department visits for adverse drug events were based on data from the 58 non-pediatric hospitals participating in the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) System, a nationally representative, size-stratified probability sample of hospitals (excluding psychiatric and penal institutions) in the United States and its territories with a minimum of 6 beds and a 24-hour emergency department (Figure 1) (33–35). As described elsewhere (5, 34), trained coders at each hospital reviewed clinical records of every emergency department visit to report physician-diagnosed adverse drug events. Coders reported clinical diagnosis, medication implicated in the adverse event, and narrative descriptions of preceding circumstances. Data collection, management, quality assurance, and analyses were determined to be public health surveillance activities by the Centers for Disease

Figure 1. Data sources and descriptions.



NAMCS = National Ambulatory Medical Care Survey (36); NEISS-CADES = National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance System (5, 33–35); NHAMCS = National Hospital Ambulatory Medical Care Survey (37). *The NEISS-CADES is a 63-hospital national probability sample, but 5 pediatric hospitals were not included in this analysis.

Control and Prevention (CDC) and U.S. Food and Drug Administration human subjects oversight bodies and, therefore, did not require human subject review or institutional review board approval.

National estimates of outpatient prescription were based on 2 cross-sectional surveys, the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS), designed to provide information on outpatient office visits and visits to hospital outpatient clinics and emergency departments (Figure 1) (36, 37). These surveys have been previously used to document the prescription rates of inappropriate medications (17, 38–40).

Definition of Potentially Inappropriate Medications

The most recent iteration of the Beers criteria (12) categorizes 41 medications or medication classes as potentially inappropriate under any circumstances (“always potentially inappropriate”) and 7 medications or medication classes as potentially inappropriate when used in certain doses, frequencies, or durations (“potentially inappropriate in certain circumstances”). For example, ferrous sulfate is considered to be potentially inappropriate only when used at dosages greater than 325 mg/d, but not potentially inappropriate if used at lower dosages.

For this investigation, we included the Beers criteria medications listed in Table 1. Because medication dose, duration, and frequency were not always available in NEISS-CADES and are not reported in NAMCS and NHAMCS, we included medications regardless of dose, duration, or frequency of use. We excluded 3 medications considered to be potentially inappropriate when used in specific formulations (short-acting nifedipine, short-acting oxybutynin, and desiccated thyroid) because NEISS-CADES, NAMCS, and NHAMCS do not reliably identify these formulations.

The updated Beers criteria identify additional medications as potentially inappropriate if they are prescribed to patients who have certain preexisting conditions. We did not include these medications because they have rarely been used in previous studies or safety measures and NEISS-CADES, NAMCS, and NHAMCS do not reliably identify preexisting conditions.

Identification of Emergency Department Visits for Adverse Drug Events

We defined an adverse drug event case as an incident emergency department visit by a patient age 65 years or older, from 1 January 2004 to 31 December 2005, for a condition that the treating physician explicitly attributed to the use of a drug or for a drug-specific effect (5). Adverse events include allergic reactions (immunologically mediated effects) (41), adverse effects (undesirable pharmacologic or idiosyncratic effects at recommended doses) (41), unintentional overdoses (toxic effects linked to excess dose or impaired excretion) (41), or secondary effects (such as falls and choking). We excluded cases of intentional self-

Table 1. Potentially Inappropriate Medications for Individuals Age 65 Years or Older*

Always potentially inappropriate†

High severity
 Amiodarone
 Amitriptyline
 Chlorpropamide
 Disopyramide
 Doxepin
 Guanadrel
 Guanethidine
 Indomethacin
 Ketorolac
 Meperidine
 Meprobamate
 Mesoridazine
 Methyldopa
 Methyltestosterone
 Mineral oil
 Nitrofurantoin
 Orphenadrine
 Pentazocine
 Thioridazine
 Ticlopidine
 Trimethobenzamide
 Amphetamines (except methylphenidate)
 Anorexiants
 Anticholinergics and antihistamines (chlorpheniramine, diphenhydramine, hydroxyzine, cyproheptadine, promethazine, tripeleminamine, dexchlorpheniramine)
 Barbiturates (except phenobarbital)
 Gastrointestinal antispasmodics (dicyclomine, hyoscyamine, propantheline, belladonna alkaloids, clidinium–chlordiazepoxide)
 Long-acting benzodiazepines (chlordiazepoxide, diazepam, flurazepam, quazepam, halazepam, clorazepate)
 Muscle relaxants and antispasmodics (methocarbamol, carisoprodol, chlorzoxazone, metaxalone, cyclobenzaprine)

Low severity
 Cimetidine
 Clonidine
 Cyclandelate
 Dipyridamole (short-acting)
 Doxazosin
 Ergot mesyloids
 Estrogens (oral only)
 Ethacrynic acid
 Isoxsuprine
 Propoxyphene

Potentially inappropriate in certain circumstances

High severity
 Fluoxetine (used daily)
 Longer half-life nonsteroidal anti-inflammatory agents (long-term use of full-dosage naproxen, oxaprozin, piroxicam)
 Short-acting benzodiazepines (lorazepam >3 mg, oxazepam >60 mg, alprazolam >2 mg, temazepam >15 mg, triazolam >0.25 mg)
 Stimulant laxatives (long-term use of bisacodyl, cascara sagrada, castor oil except in presence of opiate analgesic use)

Low severity
 Digoxin (>0.125 mg/d, except when treating atrial arrhythmias)
 Ferrous sulfate (>325 mg/d)
 Reserpine (>0.25 mg)

* Medications identified as potentially inappropriate on the basis of the updated Beers criteria, 2003 (12). Severity was defined by the combination of the likelihood that an adverse event might occur and the clinical significance of that outcome should it occur (11).

† Short-acting nifedipine, short-acting oxybutynin, and desiccated thyroid are also considered always potentially inappropriate, but they are excluded from analyses because of the inability to distinguish between long-acting (nifedipine, oxybutynin) or synthetic (L-thyroxine) formulations.

harm, therapeutic failures, therapy withdrawal, drug abuse, adverse drug events that occurred as a result of medical treatment received during the emergency department visit, and follow-up visits for a previously diagnosed adverse drug event. We defined an adverse drug event from Beers criteria medications as an emergency department visit in which a medication from **Table 1** was implicated.

Identification of Outpatient Prescription Visits

We used the NAMCS and NHAMCS public use data files for the most recent year available (2004) to identify outpatient prescription visits. We defined an outpatient prescription visit as any outpatient office, hospital clinic, or emergency department visit at which treatment with a medication of interest was either started or continued. We identified medications by generic name for those with a single active ingredient and by individual active ingredients for combination products. We categorized visits with at least 1 medication identified in **Table 1** as involving Beers criteria medications.

Statistical Analysis

Each NEISS-CADES, NAMCS, and NHAMCS case is assigned a sample weight on the basis of the inverse probability of selection (33, 42–44). We calculated national estimates of emergency department visits and prescription visits by summing the corresponding sample weights, and we calculated 95% CIs by using the SURVEYMEANS procedure in SAS, version 9.1 (SAS Institute, Cary, North Carolina), to account for the sampling strata and clustering by site. To obtain annual estimates of visits for adverse events, we divided NEISS-CADES estimates for 2004–2005 and corresponding 95% CI end points by 2. Estimates based on small numbers of cases (<20 cases for NEISS-CADES and <30 cases for NAMCS and NHAMCS) or with a coefficient of variation greater than 30% are considered statistically unstable and are identified in the tables.

To estimate the risk for adverse events relative to outpatient prescription, we divided the estimated number of emergency department visits for adverse drug events by the estimated number of outpatient visits at which implicated medications were prescribed. The 95% CI for each risk estimate incorporated variance estimates for both numerator and denominator components (45). Because we calculated these components from separate surveillance systems, they were treated as independent (and, thus, as having zero covariance).

To compare the risk for emergency department visits for adverse drug events from medications considered to be always potentially inappropriate with that from other medications, we calculated a ratio of these risks and an accompanying 95% CI (46). We applied a bias correction because of the nontrivial coefficient of variation for the denominator risk estimate (45). The 95% CI for this risk ratio incorporated variance estimates for both numerator and denominator components, which were treated as hav-

ing negligible covariance, on the assumption that there were no clinically significant associations between prescriptions or adverse drug events from commonly implicated medications and medications considered to be always potentially inappropriate.

Role of the Funding Source

Data collection from NEISS-CADES, NAMCS, and NHAMCS is funded by the CDC, and the authors conducted the collection, analysis, and interpretation of data as part of official CDC duties. The U.S. Food and Drug Administration provided additional funding for data collection but had no role in the analysis or interpretation of data or in the decision to submit the manuscript for publication.

RESULTS

On the basis of 4492 adverse drug event cases reported, an estimated 177 504 emergency department visits (95% CI, 100 155 to 254 854 visits) for adverse drug events occurred annually in 2004 and 2005. Of these, an estimated 3.6% (CI, 2.8% to 4.5%) involved Beers criteria medications categorized as always potentially inappropriate; an additional 5.2% (CI, 3.4% to 7.1%) involved medications categorized as potentially inappropriate in certain circumstances.

Patients with adverse drug events from Beers criteria medications were slightly older (mean age, 79.0 years [CI, 77.9 to 80.1 years]) than patients with adverse drug events from other medications (mean age, 77.0 years [CI, 76.7 to 77.4 years]). More adverse drug events occurred among women in both groups (**Table 2**). Compared with visits for adverse drug events due to other medications, visits for adverse drug events due to Beers criteria medications were more likely to be for adverse effects than were other types of adverse drug events and were more likely to have 2 medications implicated. The number of concomitant medications listed was similar for both groups.

Among the 41 medications or medication classes considered to be always potentially inappropriate, more than half of the estimated emergency department visits were from anticholinergics or antihistamines, nitrofurantoin, or propoxyphene (**Table 3**). More than half of cases involving nitrofurantoin were allergic reactions (14 of 25 cases).

Among medications considered to be potentially inappropriate in certain circumstances, digoxin was most commonly implicated, accounting for an estimated 3.1% of all emergency department visits for adverse drug events. The dose of digoxin involved in the adverse drug event was documented in 44 cases, and the dose was considered to be acceptable in 20 (45.5%) of these cases (≤ 0.125 mg/d).

Of the 14 medications implicated in 1% or more of estimated emergency department visits for adverse drug events, digoxin was the only medication included in the Beers criteria (**Table 3**). Nine of the 10 most commonly implicated medications may be categorized into 3 classes:

Table 2. Cases and Annual National Estimates of Emergency Department Visits for Adverse Drug Events in Individuals Age 65 Years or Older, by Patient Characteristic*

Characteristic	Emergency Department Visits from Potentially Inappropriate Medications		Emergency Department Visits from Other Medications	
	Cases, <i>n</i>	Annual National Estimate [95% CI], <i>n</i> (%)	Cases, <i>n</i>	Annual National Estimate [95% CI], <i>n</i> (%)
Potentially inappropriate medication†				
Always potentially inappropriate	159	6452 (40.9 [31.2–50.6])	–	–
Potentially inappropriate in certain circumstances	227	9308 (59.1 [49.4–68.8])	–	–
Age				
65–69 y	66	2307 (14.6 [11.4–17.9])	835	32 429 (20.0 [18.1–22.0])
70–74 y	71	2682 (17.0 [13.7–20.3])	872	32 764 (20.2 [18.7–21.8])
75–79 y	80	3409 (21.6 [15.6–27.8])	912	35 598 (22.0 [20.7–23.4])
80–84 y	77	2871 (18.2 [14.1–22.3])	768	31 352 (19.4 [18.0–20.8])
≥85 y	92	4490 (28.5 [21.2–35.8])	719	29 603 (18.3 [16.4–20.2])
Sex				
Female	270	11 029 (70.0 [65.7–74.2])	2504	98 847 (61.1 [56.5–65.7])
Male	116	4731 (30.0 [25.7–34.3])	1601	62 856 (38.9 [34.3–43.5])
Type of adverse event‡				
Unintentional overdose	129	5435 (34.5 [26.4–46.2])	1918	72 085 (44.6 [38.4–50.7])
Adverse effects	166	6876 (43.6 [36.8–50.5])	1199	49 847 (30.8 [26.9–34.7])
Allergic reaction	62	2129 (13.5 [7.1–20.0])	747	30 028 (18.6 [14.6–22.6])
Secondary effects	29	1320 (8.4 [5.1–11.6])	197	7958 (4.9 [3.7–6.1])
Vaccination reaction	0	–	45	1828 (1.1 [0.8–1.5])
Number of implicated medications				
1	276	11 275 (71.5 [66.4–76.8])	3451	136 298 (84.3 [81.3–87.2])
≥2	110	4485 (28.5 [23.2–33.6])	655	25 448 (15.7 [12.8–18.7])
Number of concurrent medications				
None	104	4004 (25.4 [9.8–41.0])	1005	40 148 (24.8 [14.9–34.7])
1–4	151	6191 (39.3 [30.4–48.2])	1496	60 101 (37.2 [32.6–41.7])
≥5	131	5565 (35.3 [23.7–47.0])§	1605	61 497 (38.0 [31.7–44.3])
Total	386	15 760	4106	161 746

* Case counts and estimates from the 2004–2005 National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance System, Centers for Disease Control and Prevention. Sex was missing for 1 case-patient.

† Medications identified as potentially inappropriate on the basis of the updated Beers criteria, 2003 (12) (Table 1). For medications considered potentially inappropriate only in certain circumstances, all emergency department visits for adverse events attributed to those medications were included regardless of the dose, frequency, or duration of use.

‡ Adverse events were categorized into 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 [e.g., falls, choking]).

§ Coefficient of variation, 33.6%.

oral anticoagulant or antiplatelet agents (warfarin, aspirin, and clopidogrel), antidiabetic agents (insulin, metformin, glyburide, and glipizide), and narrow therapeutic index agents (digoxin and phenytoin). Together, these 3 classes of medications accounted for an estimated 47.5% (CI, 40.2% to 54.8%) of all emergency department visits for adverse drug events among older adults, and we considered these commonly implicated agents together for further analyses.

Figure 2 shows the estimates of emergency department visits for adverse drug events, outpatient prescription visits, and risk for emergency department visits involving Beers criteria medications and commonly implicated agents. The estimated number of emergency department visits from just 3 medications (insulin, warfarin, and digoxin) was 9 times greater than that from Beers criteria medications

considered to be always potentially inappropriate (33.3% [CI, 27.8% to 38.7%] vs. 3.6% [CI, 2.8% to 4.5%]) (Figure 2, top). At least 1 medication considered to be always potentially inappropriate was prescribed in an estimated 10.5% (CI, 9.7% to 11.2%) of outpatient visits, whereas insulin, warfarin, or digoxin was prescribed in an estimated 2.6% (CI, 2.3% to 2.9%) of outpatient visits. All types of oral anticoagulants or antiplatelet agents, antidiabetic agents, and narrow therapeutic index agents were prescribed in an estimated 9.4% (CI, 8.4% to 10.5%) of outpatient visits (Figure 2, middle). The estimated risk for emergency department visits for adverse drug events was statistically significantly higher for insulin, warfarin, and digoxin (206 per 100 000 outpatient prescription visits [CI, 90.6 to 321]) than for Beers criteria medications considered to be always potentially inappropriate (5.6 per

Table 3. Cases and National Estimates of Emergency Department Visits for Adverse Drug Events in Persons Age 65 Years or Older, by Medication*

Medication	Emergency Department Visits for Adverse Events	
	Cases, <i>n</i>	National Estimate (95% CI), %
Potentially inappropriate medication†		
Always potentially inappropriate		
Anticholinergics and antihistamines (chlorpheniramine, diphenhydramine, hydroxyzine, promethazine)	38	0.9 (0.5–1.3)
Nitrofurantoin	25	0.5 (0.3–0.7)
Propoxyphene	23	0.5 (0.2–0.8)
Other medications	73	1.7 (1.1–2.3)
Muscle relaxants and antispasmodics (carisoprodol, cyclobenzaprine)	12	–
Clonidine	10	–
Amiodarone	8	–
Diazepam	7	–
Amitriptyline	6	–
Indomethacin	5	–
Gastrointestinal antispasmodics (belladonna alkaloids, dicyclomine, hyoscyamine)	4	–
Doxazosin	3	–
Estrogens (oral)	2	–
Ticlopidine	2	–
Trimethobenzamide	2	–
Ketorolac	1	–
Meperidine	1	–
Orphenadrine	1	–
>1 drug implicated	9	–
Potentially inappropriate in certain circumstances		
Digoxin	127	3.1 (1.6–4.6)
Short-acting benzodiazepines (alprazolam, lorazepam, temazepam)	44	0.9 (0.5–1.3)
Longer half-life NSAID (naproxen, piroxicam)	32	0.6 (0.3–0.8)
Other medications	24	0.7 (0.5–0.9)
Iron salts	14	–
Stimulant laxatives (bisacodyl, castor oil, sennosides)	4	–
Fluoxetine	2	–
>1 drug implicated	4	–
Most commonly implicated medications‡		
Warfarin	854	17.3 (12.7–21.9)
Insulin	616	13.0 (9.4–16.6)
Aspirin	232	5.7 (3.3–8.2)
Clopidogrel	173	4.7 (1.5–7.9)§
Digoxin	130	3.2 (1.6–4.7)
Metformin	103	2.3 (1.4–3.2)
Glyburide	98	2.2 (0.9–3.5)
Acetaminophen–hydrocodone	76	1.7 (1.0–2.5)
Phenytoin	78	1.5 (0.8–2.3)
Glipizide	57	1.5 (0.8–2.1)
Levofloxacin	63	1.4 (1.1–1.8)
Lisinopril	62	1.4 (0.8–2.0)
Trimethoprim–sulfamethoxazole	52	1.3 (0.9–1.7)
Furosemide	48	1.2 (0.6–1.8)

* Case counts and estimates from the 2004–2005 National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance System, Centers for Disease Control and Prevention. NSAID = nonsteroidal anti-inflammatory drug.

† Medications identified as potentially inappropriate on the basis of the updated Beers criteria, 2003 (12) (Table 1). For medications considered potentially inappropriate only in certain circumstances, all emergency department visits for adverse events attributed to those medications were included regardless of the dose, frequency, or duration of use.

‡ Drugs implicated in >1% of estimated emergency department visits. For 337 cases, 2 medications were implicated in a single emergency department visit for an adverse drug event.

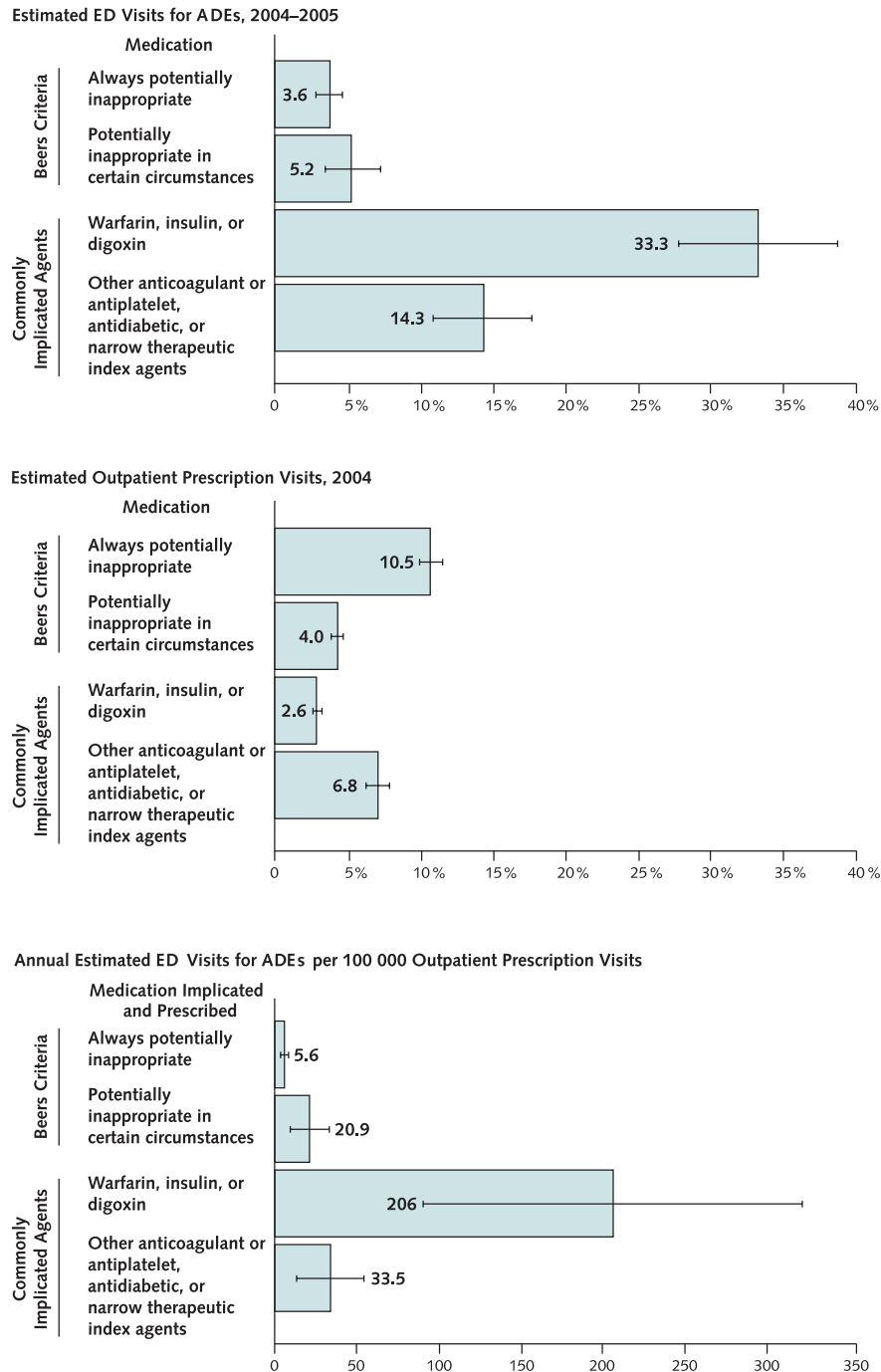
§ Coefficient of variation, 34.2%.

100 000 outpatient prescription visits [CI, 3.3 to 7.9]) or for Beers medications considered to be potentially inappropriate in certain circumstances (20.9 per 100 000 outpatient prescription visits [CI, 9.0 to 32.9]) (Figure 2, *bottom*). The ratio of the risk for emergency department visits

per 100 000 outpatient prescription visits for insulin, warfarin, and digoxin to that for medications considered to be always potentially inappropriate was 37, with a bias-corrected estimate of 35 (CI, 9.6 to 61).

Most cases of adverse events from insulin, warfarin,

Figure 2. National estimates of emergency department (ED) visits for adverse drug events (ADEs) (top), outpatient prescription visits (middle), and risk (bottom) for persons age 65 years or older.



Data are from the 2004–2005 National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance System (*top*) and the 2004 National Ambulatory Medical Care Survey and National Hospital Ambulatory Care Survey (*middle*), Centers for Disease Control and Prevention. Risks for adverse events (*bottom*) are estimated by dividing the estimated number of ED visits for ADEs (*top*) by the estimated number of outpatient visits at which implicated medications were prescribed (*middle*). Medications are identified as potentially inappropriate on the basis of the updated Beers criteria, 2003 (12) (Table 1). For medications considered potentially inappropriate only in certain circumstances, all ED visits for ADEs attributed to those medications were included regardless of the dose, frequency, or duration of use. Commonly implicated agents include the 3 medications (warfarin, insulin, and digoxin) and 3 medication classes (oral anticoagulant or antiplatelet, antidiabetic, and narrow therapeutic index agents) that most commonly caused ED visits for ADEs (Table 3). Oral anticoagulant or antiplatelet agents, other than warfarin, included aspirin, clopidogrel, ticlopidine, and cilostazol. Antidiabetic agents, other than insulin, included oral hypoglycemics. Narrow therapeutic index agents, other than digoxin, included phenytoin, carbamazepine, primidone, valproic acid, lithium, theophylline, and L-thyroxine. Bars represent 95% CIs.

and digoxin were dose-related, and specific manifestations are further described in the **Appendix Table** (available at www.annals.org). Of the cases attributed to warfarin, 73.0% involved clinically evident bleeding and 44.2% required hospitalization. Of the cases attributed to insulin, 95.4% were due to hypoglycemia, 24.1% involved loss of consciousness or seizure, and 25.1% required hospitalization. The cases attributed to digoxin involved various effects, and 80.2% of them required hospitalization.

DISCUSSION

We believe that our investigation is the first using nationally representative data to estimate the number of and risk for adverse events involving Beers criteria medications and to place these adverse events in context of those involving other medications. We found that relatively few emergency department visits for adverse drug events among older adults (3.6%) were caused by Beers criteria medications considered to be always potentially inappropriate, despite these medications being prescribed in 10.5% of ambulatory care visits. Monitoring or intervention programs targeting Beers criteria medications categorized as being potentially inappropriate only when used in certain doses, durations, or frequencies have not been as widely described, but this may be a goal for future measures. However, even after including all adverse drug events from these additional medications regardless of dose, duration, or frequency administered, we found that fewer than 10% of emergency department visits for adverse drug events were attributable to Beers criteria medications.

On the other hand, we found that 9 of the 10 medications that most commonly caused emergency department visits for adverse drug events among older adults were in 3 medication classes (oral anticoagulants or antiplatelet agents, antidiabetic agents, and narrow therapeutic index agents). Together, these 3 medication classes caused nearly half of all emergency department visits for adverse drug events but were prescribed in only 9.4% of outpatient visits. Other studies of adverse drug events in older adults have also found that high percentages of adverse drug events are caused by these medication classes (9, 47, 48). The most commonly implicated medications from these classes (warfarin, insulin, and digoxin) accounted for one third of all emergency department visits for adverse drug events among older adults, and the risk for emergency department visits for adverse drug events involving these medications was clinically and statistically significantly higher than that involving Beers medications considered to be always potentially inappropriate (206 vs. 5.6 per 100 000 outpatient prescription visits; bias-corrected risk ratio, 35 [CI, 9.6 to 61]).

Despite the high number of emergency department visits for adverse drug events and the high risk per outpatient prescription visit for warfarin, insulin, and digoxin, these are often critical medications that should not be labeled as “inappropriate” for use in older adults. However,

the fact that the benefits of anticoagulation with warfarin or intensive blood glucose control are considered to outweigh the risks (49–51) does not mean we should consider large numbers of emergency department visits for bleeding or hypoglycemia acceptable for our patients. Instead, our findings suggest that, because of the high risk for adverse events and the common outpatient use of insulin, warfarin, and digoxin, even small improvements in the use of these medications have greater potential for reducing the burden of serious adverse drug events among older Americans, as measured by emergency department visits, than do large reductions in the prescription of lower-risk medications, such as those considered to be always potentially inappropriate by the Beers criteria.

Our analytic approach may have overestimated the number of emergency department visits from Beers criteria medications and underestimated that from other medications. First, allergic reactions accounted for 13.5% of emergency department visits involving Beers criteria medications. Although allergic reactions are certainly adverse drug events, they are rarely the basis for categorizing medications as potentially inappropriate. Second, for estimates of adverse drug events from medications considered to be potentially inappropriate when used in certain doses, durations, or frequencies, we included all adverse drug events, even if an appropriate dose was used. Among the adverse drug event cases from digoxin for which the dose was known, about 45% involved an acceptable dose. Finally, NEISS-CADES could be biased toward detecting acute, well-known medication effects or effects for which testing is available in the emergency department, such as hypoglycemia from an insulin overdose or hypocoagulability due to warfarin therapy. However, in an evaluation of 6 NEISS-CADES hospitals, these events were found to be substantially underreported rather than overreported (35).

The Beers criteria have received renewed attention as a quality and safety measure because prescription data can be easily collected using administrative sources, and substituting a superior medication for an inferior one is an elegant clinical intervention. A MEDLINE search from 1996 to April 2007 identified more than 50 investigations documenting widespread potentially inappropriate prescriptions in community, long-term care, and hospital settings throughout the world. Potentially inappropriate prescriptions have recently been associated with increased health care costs and may be a marker for poor-quality care (22, 24); however, population-based evidence of a causal linkage between these prescribing practices and specific adverse events is lacking (52). Although some studies in certain settings demonstrated an epidemiologic association between Beers criteria medications and general adverse outcomes (such as hospitalizations) (26, 53), other studies did not (54, 55). A recent systematic review concluded that Beers criteria medications were associated with some adverse health effects, but the studies analyzed were too heterogeneous to support formal meta-analysis (56). Thus, if

the goal is to reduce adverse events, then selection bias, confounding by indication, and uncontrolled confounding should be carefully considered before basing performance measures and safety interventions on epidemiologic associations that are in question (54, 57, 58).

Some have questioned the utility of the Beers criteria on clinical grounds (59–61) and have proposed modifications (18, 62). The Beers criteria or other measures, such as polypharmacy, may be helpful indicators of prescription quality, but these seem to have limited concordance in identifying at-risk patients (63). Thus, use of Beers criteria medications may be one indicator of poor-quality prescribing practices, but measures intended to maximize safety for the most patients should focus on medications clinically linked to common, severe adverse outcomes.

Our findings emphasize the need to determine the most effective interventions for common, severe outpatient adverse drug events and to identify new approaches (64). Both the U.S. Food and Drug Administration and the National Patient Safety Foundation in the United Kingdom have recently made improving anticoagulant safety a top priority (65–67), and various interventions to prevent adverse drug events from warfarin have been evaluated (68) and have been shown to be successful (69–71). On the other hand, approaches to preventing hypoglycemia are largely based on poor-quality evidence (72). Although the antiplatelet agents aspirin and clopidogrel caused more emergency department visits than did digoxin, we highlighted digoxin together with insulin and warfarin because most adverse effects of digoxin were severe, with more than 80% of cases requiring hospitalization, and the burden of these adverse events, such as those from warfarin and insulin, may be mitigated with improved therapeutic drug monitoring (73, 74).

Our findings should be interpreted in the context of several important limitations. First, we estimated only adverse events resulting in emergency department visits. Adverse events diagnosed and treated in other settings (for example, in primary care offices, in urgent care centers, or during hospitalizations) or not treated in any health care facility were not included. Adverse drug events manifested by the gradual onset of symptoms or uncommon adverse effects are unlikely to be diagnosed in emergency department settings. Although such adverse events are indeed important, focusing on common, severe adverse events, such as those requiring emergency care, is reasonable from a public health perspective.

Second, we examined adverse event data only from 2004 and 2005. Thus, the promulgation of the Beers criteria might have been successful in reducing adverse events that previously were more common, although the prescription of Beers criteria medications has changed little in the past decade (75).

Third, because NEISS-CADES relies on documentation of adverse drug events by the treating physician, it is probably less sensitive than research studies involving chart

review by specially trained pharmacists or physicians, computer-generated signals, patient interviews, or combination approaches to identify undiagnosed and undocumented adverse drug events.

Fourth, NAMCS and NHAMCS estimates of outpatient prescriptions are based on up to 8 medications that were provided, prescribed, or continued at ambulatory medical care visits, as reported by medical providers, and these surveys do not collect data on dose, regimen, or adherence. Other estimates of outpatient prescriptions based on prescriptions filled, dose equivalents, or patient surveys might provide different estimates of medication use.

Finally, in calculating the 95% CIs for emergency department visits and prescription visits, we assumed no patient-level clustering effects in estimating the variances of the counts; however, any related bias in the variance estimates is unlikely to account for the statistical significance of the primary comparisons among emergency department visit or risk estimates. In calculating the 95% CI for the risk ratio, we assumed no covariance for the prescription of and adverse drug events from the 3 commonly implicated medications (warfarin, insulin, and digoxin) and from the medications considered to be always potentially inappropriate. It is conceivable that the prescription of and adverse drug events from warfarin, insulin, and digoxin may be associated with receiving 1 of the medications considered to be always potentially inappropriate. However, any unrecognized covariation is also unlikely to account for the statistical significance of the ratio estimate.

Clinicians should continue to use criteria of medication appropriateness to optimize medication selection for their older patients. However, these national public health surveillance data suggest that there may be considerable opportunity to reduce adverse events in older patients through interventions that improve the use of anticoagulants, antidiabetic agents, and narrow therapeutic index medications.

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Appendix Table. Emergency Department Visits for Adverse Events from Warfarin, Insulin, and Digoxin in Individuals Age 65 Years or Older, by Adverse Event Manifestation*

Adverse Event Manifestation	Cases, n (%)
Warfarin	
Hemorrhage†	501 (73.0)
Intracranial hemorrhage	20 (2.9)
Hemoptysis	13 (1.9)
Gastrointestinal hemorrhage	124 (18.1)
Genitourinary hemorrhage	49 (7.1)
Epistaxis	124 (18.1)
Skin or wound hemorrhage	127 (18.5)
Other types of hemorrhage	44 (6.4)
Elevated protime/INR only	123 (17.9)
Other or unspecified effect	62 (9.0)
Insulin	
Hypoglycemia†	554 (95.4)
With loss of consciousness or seizure	140 (24.1)
With altered mental status	197 (33.9)
With other neurologic sequelae	76 (13.1)
With cardiovascular sequelae	16 (2.8)
With other or unspecified sequelae	125 (21.5)
Other or unspecified effect	27 (4.6)
Digoxin	
Cardiovascular effects only	24 (22.6)
Neurologic effects only	25 (23.6)
Gastrointestinal effects only	11 (10.4)
Multiple system effects	29 (27.4)
Other or unspecified effect	13 (12.3)
Elevated digoxin level only	4 (3.8)

* Case counts from the 2004–2005 National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance Project, Centers for Disease Control and Prevention. Only cases in which warfarin (686 cases), insulin (581 cases), or digoxin (106 cases) were the only drugs implicated in the adverse event are included. INR = international normalized ratio.

† Adverse event types are mutually exclusive and were assigned hierarchically. For example, a case in which a patient experienced both rectal bleeding and hematuria during warfarin therapy would be categorized as gastrointestinal hemorrhage.