Risk Factors for Adverse Drug Events Among Older Adults in the Ambulatory Setting

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OBJECTIVES: To gather information on patient-level factors associated with risk of adverse drug events (ADEs) that may allow focus of prevention efforts on patients at high risk.

DESIGN: Nested case-control study.

SETTING: Large multispecialty group practice in New England.

PARTICIPANTS: All Medicare enrollees cared for by a multispecialty group practice during 1 year (N = 30,397 person-years from July 1, 1999, through June 30, 2000). For each patient with an ADE, a control was randomly selected.

MEASUREMENTS: Data were abstracted from medical records on age, sex, comorbidities, and medication use at the time of the event.

RESULTS: ADEs were identified in 1,299 older adults. Independent risk factors included being female and aged 80 and older. There were dose-response associations with the Charlson Comorbidity Index and number of scheduled medications. Patients taking anticoagulants, antidepressants, antibiotics, cardiovascular drugs, diuretics, hormones, and corticosteroids were at increased risk. In the analysis of preventable ADEs, the dose-response relationship with comorbidity and number of medications remained. Patients taking nonopioid analgesics (predominantly nonsteroidal antiinflammatory drugs and acetaminophen), anticoagulants, diuretics, and anti-seizure medications were at increased risk.

CONCLUSION: Prevention efforts to reduce ADEs should be targeted toward older adults with multiple medical conditions or taking multiple medications, nonopioid analgesics, anticoagulants, diuretics, and antiseizure medications. **J Am Geriatr Soc 52:1349–1354, 2004.**

Key words: adverse drug events; risk factors; ambulatory care

Adverse drug events (ADEs) occur during the provision of medical care in the United States in all clinical settings.[1–3] Recent reports of ADE rates have served to stimulate increased focus on efforts to improve patient safety.[4] Most of the published studies of the incidence and preventability of ADEs have been performed in the inpatient setting. Much less information has been available about the occurrence of ADEs outside of the hospital. In the ambulatory setting, older adults may be at particular risk of ADEs because of the intensity of their use of prescribed medications. A recent national survey of the noninstitutionalized U.S. population indicated that more than 90% of persons aged 65 and older use at least one medication per week,[5] more than 40% use five or more different medications per week, and 12% use 10 or more different medications. It was recently reported that ADEs are common and often preventable in older persons in the ambulatory clinical setting. The rate of ADEs was 50.1 per 1,000 person-years; 28% of ADEs were found to be preventable.[6]

As strategies for preventing and reducing the effect of these ADEs in the outpatient setting are developed and implemented, an important component will be the identification of patients at special risk. A frequently proposed strategy is the use of computerized physician order entry[7,8] accompanied by automated clinical decision support systems[9–11] that allow healthcare providers to take into account the individual's level of risk in their decisions about prescribing, delivering, and monitoring drug therapy. An understanding of the factors associated with heightened risk for ADEs would enable the designers of these systems to

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include special warnings to healthcare providers. To support this development, a case-control study, nested within the study of the incidence and preventability of ADEs described above,[6] was performed to identify patient-level factors associated with ADEs in older adults.

METHODS

The study was conducted within a large multispecialty group practice in New England. The multispecialty group practice provides care to more than 30,000 persons aged 65 and older, nearly 90% of whom are enrolled in a Medicare+Choice Plan (Medicare risk contract with the health plan), with the remainder being traditional fee-for-service Medicare enrollees.

Subjects for this study included all persons aged 65 and older receiving healthcare services in the ambulatory setting. Residents of long-term care facilities were excluded from the study. The study period ran from July 1, 1999, through June 30, 2000.

The institutional review boards of the University of Massachusetts Medical School and of the group practice and the associated health maintenance organization approved the project, which was implemented under the auspices of the health plan and medical group quality management committees as part of peer-review and quality-improvement activities.

ADEs were defined as injuries resulting from the use of drugs. This definition for an ADE is consistent with definitions used in previous studies.[1,3] ADEs may have resulted from medication errors (i.e., errors in prescribing, dispensing, patient adherence, and monitoring) or from adverse drug reactions (ADRs) in which no error was involved.

Possible drug-related incidents that occurred in the outpatient setting were detected through multiple methods: reports from healthcare providers, review of hospital discharge summaries, review of emergency room notes, computer-generated signals, automated free-text review of clinic notes, and review of administrative incident reports concerning medication errors. Ambulatory medical records were selected for review based on information from the detection methods listed above. Trained clinical pharmacist investigators performed medical record reviews and abstractions.

A clinical pharmacist investigator presented possible drug-related incidents to pairs of physician-reviewers selected from among four of the authors (JG, DWB, LH, JR) who classified them independently as to whether they were ADEs. Physician reviewers considered the temporal relation between the drug exposure and the event, as well as whether the event reflected a known effect of the drug. For all events classified as ADEs, reviewers also determined preventability. Reviewers classified an ADE as preventable if it was due to an error and was preventable by any means available.[6] The physician-reviewers were compared on all of their initial assessments. Interrater reliability for initial judgments was calculated using the kappa statistic. For judgments about the presence of an ADE, the kappa value was 0.81; for preventability, the kappa value was 0.67. A kappa value of 0.6 to 0.8 reflects substantial agreement and a value of 0.8 to 1.0 is considered almost perfect.[12]

Cases included all individuals who experienced an ADE during the study period. For those with multiple ADEs, only the first ADE was included, and all risk factor data were collected as of the date of that event. During the year of observation, 1,523 ADEs were identified in 1,299 individuals.

Preventable ADEs were analyzed separately. For this portion of the study, cases included all individuals who experienced a preventable event. Risk factor data were collected as of the date of the first preventable ADE. Of the 1,299 subjects with an ADE, 383 had at least one ADE that was classified as preventable.

For each case, a control was randomly selected from all individuals aged 65 and older who had an outpatient visit and drug dispensing within the month before the case's ADE. For subjects whose preventable ADE was not the first event, an additional control was selected based on the date of the preventable ADE. Risk factor information was collected for the case and controls as of the date of the event. All individuals who had not yet had an ADE at the time of the event were eligible to serve as controls.

Information on potential risk factors for cases and controls was collected through chart review using standardized forms. Data included sex and age calculated from date of birth. Age was organized into 5-year categories. Burden of illness was assessed using the Charlson Comorbidity Index[13] (categorized as originally developed: 0, 1–2, 3–4, and 5). Agreement between chart abstractors on categories of the Charlson Comorbidity Index was high; in a sample of 10 charts abstracted by each of the four abstractors, the Kendall coefficient of concordance was 0.71. Information on medication use at the time of the event included the number of current regularly scheduled medications, categorized as 0 to 1, 2 to 4, 5 to 7, and 8 or more. For categories of numbers of medications, the Kendall coefficient of concordance was 0.72. Regularly scheduled drugs were also categorized into the following drug classes: Alzheimer's disease treatments, antibiotics/antiinfectives, anticoagulants, antidepressants, antigout therapy, antihistamines, antineoplastics, antiparkinsonians, antiplatelets, antipsychotics, anti-seizure medications, cardiovascular drugs, antihyperlipidemics, diuretics, disease modifying antirheumatic drugs, gastrointestinal medications, hormones, hypoglycemics, immunomodulators, muscle relaxants, nonophthalmic topicals and dermatologics, nonopioid analgesics (predominantly nonsteroidal antiinflammatory drugs and acetaminophen), nutrients/supplements, ophthalmics, opioids, osteoporosis medications, respiratory medications, sedatives/hypnotics, corticosteroids, and thyroid medications.

ANALYSIS

Analyses began with the calculation of chi-squares and *P*-values for each categorical variable. Subsequently, separate multivariate models were constructed using all ADEs and preventable ADEs as the outcome with stepwise logistic regression using SAS (SAS Institute, Inc., Cary, NC). Variables that were significantly associated with case/control status at $P \leq .05$ and with prevalence of at least 5% in the case or control group were considered for inclusion. Correlations between potential risk factors were assessed, and any highly correlated variables were analyzed in separate

models. Age categories and sex were forced into all models. Variables were retained in the model if they were found to have *P*-values of .05 or less. Interactions in the optimum models were assessed. The predictive discrimination of the optimum models separately for all ADEs and preventable ADEs were assessed using receiver operating characteristic (ROC) curves to produce estimates of the areas under the curves and 95% confidence intervals (CIs).

RESULTS

There were 1,299 individuals who experienced an ADE and 1,299 controls (Table 1). The two groups had similar proportions of women, but subjects who experienced an ADE were significantly more likely ($P < .001$) to be older, have a higher score on the Charlson Comorbidity Index, take more medications, and be taking medications in the following specific categories: anticoagulants, antidepressants, antibiotics/antiinfectives, antineoplastics, cardiovascular drugs, diuretics, antiseizure medications, gastrointestinal drugs, gout treatment, hematological drugs, hormones, hypoglycemics, opioids, respiratory drugs, corticosteroids, and thyroid treatments. Cases were less likely to be taking a nutrient or other supplement.

To identify independent correlates of ADEs, a multivariate model was developed using stepwise, backward logistic regression (Table 2). Factors independently correlated with higher risk of having an ADE included being female and aged 80 and older. There were dose-response relationships with the Charlson Comorbidity Index and the number of scheduled medications, with tests for trend significant for each in the full multivariate model. Drugs significantly associated with having an ADE were anticoagulants, antidepressants, antibiotic/antiinfectives, cardiovascular drugs, diuretics, hormones, and corticosteroids. The model had moderate predictive power, with the area under the ROC curve equal to 0.74 (95% CI = 0.72–0.76) Possible problems with collinearity in variables in the model were assessed; none were found. Interactions were assessed; none were significant.

Univariate analyses were also performed to identify variables correlated with the presence of a preventable ADE (Table 1). Subjects with preventable ADEs were significantly more likely to be older, have a higher score on the Charlson Comorbidity Index, take more medications, and take medications in the following categories: nonopioid analgesics, anticoagulants, antidepressants, antineoplastics, cardiovascular drugs, diuretics, antiseizure medications, gastrointestinal drugs, gout treatment, hematological drugs, hypoglycemics, opioids, respiratory drugs, and corticosteroids. They were less likely to be using a nonophthalmic topical or dermatological medication.

Independent predictors of a preventable ADE were identified using backward stepwise logistic regression (Table 3). There was a dose-response association between the Charlson Comorbidity Index and number of scheduled medications. The drugs independently associated with having a preventable ADE were nonopioid analgesics, anticoagulants, diuretics, and antiseizure medications. Use of topical and dermatological medications was associated with lower risk of having an ADE. The predictive power of this model was somewhat higher than the model for all events (area under the ROC curve = 0.80, CI = 0.77–0.83).

DISCUSSION

A number of patient-level factors were found to be associated with ADEs and preventable ADEs. Some of these factors may be modifiable; in particular, greater numbers of regularly scheduled medications were associated with occurrence of ADEs and preventable ADEs, with a dose-response relationship. This association remained when age, sex, and comorbidity were controlled for. Several categories of medications were also associated with increased risk; anticoagulants and diuretics were associated with all ADEs and with those that were preventable, whereas nonopioid analgesics and antiseizure medications were associated specifically with preventable ADEs. Scores on the Charlson Comorbidity Index were associated with all ADEs and with those that were preventable, with a strong dose-response relationship, which remained significant after controlling for number of medications, age, and sex. Being aged 80 and older was associated with a small but significant risk of having an ADE, but that factor did not attain significance in the multivariate analysis of risk factors for preventable ADEs.

The intent of this study was to better define individual factors associated with high risk of ADEs, with the ultimate goal of supporting interventions that prevent ADEs or that enhance response to individuals who have suffered events to lessen their effect. The focus was on commonly noted factors, such as the type and number of medical conditions and drugs, which are often maintained in automated patient data and can be integrated into decision support systems for physicians, nurses, and pharmacists.

Previous studies have examined individual factors associated with ADEs or ADRs in a variety of settings, including ambulatory care,[14–19] admissions to emergency departments and hospitals,[20–25] and nursing homes.[26,27] These studies differ in their methods of identifying ADEs, their inclusion of all ADEs or only ADRs that are not associated with error, their choice of groups for comparative analyses, the range of ages included, the locations and countries in which the studies were set, and the variables examined. Previous studies in the ambulatory setting have relied on self-report by patients,[14,15,17,19] specific notes in patient charts,[16] or use of ADR codes in electronic reports by physicians,[18] and none have distinguished preventable ADEs. In most instances, the findings of these studies paralleled the findings of the current study: higher overall risk of ADEs is associated with larger numbers of medications and indicators of poorer health. Two studies did not find an association between ADEs and number of medications. One of these was based in a high-risk population, all of whom were taking five or more scheduled medications;[17] the other was a small study in which only 47 patients were identified with an ADE, limiting its power to detect associations.[16]

Studies of frail older adults receiving home health care or residing in nursing homes have found associations between ADEs and number of medications,[26,27] as have several studies of patients admitted to emergency departments and hospitals.[20–24] A few studies assessed comorbidity or

Table 1. Characteristics of Subjects with Adverse Drug Events and Controls

Characteristic	All Adverse Drug Events			Preventable Adverse Drug Events		
	Case n = 1,299	Control n = 1,299	*P*-value	Case n = 383	Control n = 383	*P*-value
Age, mean	77.1	75.8	<.01	77.5	75.6	<.01
Age, n						
65–69	210	281	<.01	50	80	<.01
70–74	306	378		87	106	
75–79	343	289		104	96	
≥80	440	251		142	101	
Female, n	786	747	.12	219	240	.12
Charlson Comorbidity Index, n						
0	313	675	<.01	63	189	<.01
1–2	582	485		172	151	
3–4	284	109		105	33	
≥5	120	30		43	10	
Medications, n						
0–1	53	220	<.01	14	64	<.01
2–4	390	584		98	167	
5–7	498	374		250	111	
≥8	358	121		121	41	
Current medications, n						
Alzheimer disease	9	8	.81	2	2	1.00
Analgesic, nonopioid*	136	117	.21	58	37	.02
Anticoagulant	270	102	<.01	91	25	<.01
Antidepressant	245	139	<.01	73	46	<.01
Antihistamine	38	56	.06	9	15	.21
Anti-hyperlipidemic	301	280	.32	78	88	.38
Antibiotic/antiinfective	303	218	<.01	74	67	.51
Antigout	71	47	.02	37	17	<.01
Antineoplastic	61	33	<.01	19	9	.05
Antiparkinsonian	16	17	.86	3	4	.70
Antiplatelets	381	363	.44	106	121	.24
Antipsychotic	28	18	.14	9	3	.08
Anti-seizure	64	34	.02	30	6	<.01
Cardiovascular	988	735	<.01	309	216	<.01
Diuretic	630	374	<.01	230	117	<.01
Disease-modifying antirheumatic drugs	13	7	.18	1	1	1.00
Gastrointestinal	354	225	<.01	100	63	<.01
Hematologic	20	3	<.01	8	0	<.01
Hormone	125	96	.04	28	24	.57
Hypoglycemics	303	173	<.01	103	50	<.01
Immunomodulator	2	0	.16	0	0	
Miscellaneous	15	9	.22	7	4	.36
Muscle relaxant	49	41	.39	18	12	.26
Nutrient/supplement	487	414	<.01	154	137	.21
Ophthalmic	129	112	.25	44	39	.56
Opioids	45	25	.02	18	6	.01
Osteoporosis	59	56	.78	14	15	.85
Respiratory	193	125	<.01	61	38	.01
Sedative/hypnotic	72	69	.80	18	24	.43
Corticosteroid	151	68	<.01	38	21	.02
Thyroid	163	131	.05	51	42	.32
Topical/dermatological	61	66	.65	13	26	.03

* Predominantly nonsteroidal antiinflammatory drugs and acetaminophen.

number of current medical problems and found associations with ADEs.[20,26,27] For studies set outside of the nursing home, the comparison groups were other patients being admitted or hospitalized, rather than a general population. This limitation makes it difficult to apply the results of these studies to the ambulatory setting, with its much broader

Table 2. Independent Risk Factors for Having an Adverse Drug Event

Risk Factor	Odds Ratio	95% Confidence Interval
Age		
65–69	1.0	referent
70–74	0.96	0.74–1.2
75–79	1.2	0.94–1.6
≥80	1.3	1.0–1.7
Female	1.2	1.0–1.5
Charlson Comorbidity Index		
0	1.0	referent
1–2	2.0	1.6–2.4
3–4	3.4	2.5–4.5
≥5	5.0	3.2–7.9
Number of scheduled medications		
0–1	1.0	referent
2–4	1.8	1.2–2.5
5–7	2.2	1.5–3.2
≥8	2.9	1.9–4.6
Current medications		
Anticoagulant	1.8	1.4–2.4
Antidepressant	1.5	1.1–1.9
Antibiotic/antiinfective	1.6	1.3–2.0
Cardiovascular	1.4	1.1–1.7
Diuretic	1.3	1.1–1.6
Hormone	1.5	1.1–2.1
Corticosteroid	1.5	1.1–2.1

population. The only study the authors have identified that assessed factors associated with drug-related hospitalizations in a community-based population did not assess number of medications or comorbidity.[25]

Advanced age has been suggested to be a potential risk factor for ADEs and was found to be associated in several studies.[14,15,21,24,25] Of these studies, in only one was the population limited to those aged 65 and older, and that study found a relationship between age and self-reported ADEs only in women.[25] The increased number of comorbidities and regularly scheduled medications associated with advanced age may largely explain the apparent effect of age. Few studies have controlled for these. These multivariate analyses of a population aged 65 and older showed an association only with aged 80 and older.

This study showed that older adults taking drugs within several specific classes were at higher risk of having an ADE. The analyses of the relationship between drug classes and ADEs did not focus on identifying drugs that were directly responsible for events. The authors were interested in using drugs as markers to identify patients at high risk by comparing the drug use patterns of those who experienced ADEs with those of a comparison group without ADEs. It was hypothesized that these drugs might have been serving as proxies for the medical condition that they were prescribed to treat or might be acting as promoters of adverse effects. One example of this is the finding of a lower risk in patients using topical or dermatological agents. Use of these medications may be a proxy for the individual's overall health or attention to self-care or the approach of the physician.

This study had several limitations. It was based in one large group practice; physician prescribing and monitoring patterns specific to this group could have colored the results. The approach used to identify and classify ADEs and preventable ADEs was based on evaluation of an extensive range of signals, followed by independent classification by two physicians. Only those events classified as ADEs with a high confidence level were included. This limited events to those with very high probability and potentially led to the exclusion of some ADEs. Thus, the findings may be biased toward risk factors for events that are most clearly associated with medication use. Strengths of this study include its setting in a population of ambulatory elders with controls drawn randomly from that population. The age and sex distribution of the population in which this study was set mirrors the overall U.S. population aged 65 and older.[6] The methods used to identify and classify ADEs were thorough.[6] Inclusion of preventable ADEs and their separate analysis allowed us to distinguish factors that may be used to estimate risk in older adults at a point when events may be prevented.

The results have several implications for preventing ADEs. Medication regimens of older persons should be carefully assessed, with periodic review of indications for therapy. Prevention efforts should be targeted toward those with multiple medical conditions or taking multiple medications, nonopioid analgesics, anticoagulants, diuretics,

Table 3. Independent Risk Factors for Having a Preventable Adverse Drug Event

Risk Factor	Odds Ratio	95% Confidence Interval
Age		
65–69	1.0	referent
70–74	1.2	0.73–2.1
75–79	1.1	0.67–1.9
≥80	1.5	0.92–2.6
Female	0.85	0.60–1.2
Charlson Comorbidity Index		
0	1.0	referent
1–2	2.3	1.6–3.5
3–4	5.2	3.0–9.0
≥5	7.5	3.3–17.0
Number of scheduled medications		
0–1	1.0	referent
2–4	1.7	0.86–3.3
5–7	2.4	1.2–4.9
≥8	3.1	1.4–6.9
Current medications		
Analgesic, nonopioid*	2.0	1.2–3.3
Anticoagulant	3.0	1.8–5.1
Diuretic	2.0	1.4–2.8
Anti-seizure	6.0	2.3–15.6
Topical/dermatological	0.39	0.17–0.89

*Predominantly nonsteroidal antiinflammatory drugs and acetaminophen.

and anti-seizure medications. In the ambulatory setting, patient education should play an important role in prevention efforts. Providers should try to ensure that patients at risk fully understand instructions for using their medications and are able to recognize and report early signs of adverse events. An additional strategy is to engage the clinical pharmacist in the care of these high-risk patients.[28] Computerization of prescribing and monitoring probably represents the most potent prevention strategy,[10] although its effect in the ambulatory setting has not been adequately evaluated. The findings of the current study suggest that it will be important to link computerized physician order entry systems to electronic files containing patient-specific data so that decision support systems can identify patients at risk. With such systems in place, it will be possible to identify and target patients at greatest need for increased levels of scrutiny.

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