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Do Geriatric Conditions Increase Risk of Adverse Drug Reactions in Ambulatory Elders? Results From the VA GEM Drug Study

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Background. Many clinicians prescribe cautiously to older adults with common geriatric conditions for fear of causing adverse drug reactions (ADRs). However, little is known about the association between these conditions and risk of ADRs.

Methods. Using data from the VA Geriatric Evaluation and Management Drug Study, we determined any, preventable, and serious ADRs in 808 elders for 12 months after hospital discharge using a validated process involving patient self-report and chart review adjudicated by two health care professionals. Eight common geriatric conditions (activities of daily living, dementia, incontinence, falls, difficulty ambulating, malnourishment, depression, and prolonged bed rest) were evaluated at study baseline through self-report and structured assessments. We used Poisson regression to model the relationship between these geriatric conditions and ADRs.

Results. Participants had a mean of 2.9 ± 1.2 geriatric conditions. Over the 12-month follow-up period, 497 ADRs occurred in 269 participants, including 187 ADRs considered preventable and 127 considered severe. On multivariable analyses, participants with dependency in one or more activities of daily living were less likely to suffer ADRs than those who were fully independent (incidence rate ratio: 0.78, 95% confidence interval = 0.62–1.00). None of the other seven geriatric conditions assessed were associated with ADR risk. Results were similar for preventable and serious ADRs, although participants with a history of falls were more likely to develop serious ADRs (incidence rate ratio: 1.49, 95% confidence interval = 1.00–2.21).

Conclusions. Many geriatric conditions were not associated with risk of ADRs. Although it is prudent to prescribe judiciously in patients with these conditions, excessive caution may not be warranted.

Key Words: Adverse drug reactions—Geriatric syndromes—Drug utilization

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ADVERSE drug reactions (ADRs) are common and comprise a major source of morbidity in older adults. However, few risk factors other than use of multiple medications have consistently been demonstrated to increase risk of ADR (1,2,3,4). This paucity of known risk factors limits the ability of clinicians to prospectively identify patients at higher risk of ADRs and thus inform decisions about drug treatment and the frequency and intensity of side-effect monitoring.

Geriatric syndromes and other markers of vulnerability in older adults are potentially important risk factors for ADRs. Anecdotal experience suggests that many clinicians use extra caution in prescribing drugs to vulnerable elders out of fear that such patients are at higher risk of suffering harms from medication use (5,6). This suspicion may be well grounded at the clinical and pharmacological levels. Pharmacokinetic studies of plasma aspirin esterase, an enzyme involved in phase 1 drug metabolism, have demonstrated a decline in enzyme activity in older adults with mobility impairment and dependency in activities of daily living (ADLs) compared with their more robust contemporaries (7). Similar patterns of frailty-associated declines in drug metabolism have been observed for several drugs, potentially leading to increased serum and tissue levels and an increased risk of drug toxicity (8,9,10).

In addition, to the extent that geriatric syndromes and other signs of vulnerability can be markers of frailty, the theoretical underpinnings of frailty support as association with elevated risk of ADRs (11,12). Frailty is commonly understood to represent decreased physiologic and/or cognitive reserve, limiting one's ability to successfully compensate when challenged with a threat to homeostasis (13,14). Many medications are designed to alter homeostasis, for example, by altering cardiac or vascular function or changing neurotransmitter function in the central nervous system. Thus, there are good grounds to believe that frail elders may be at greater risk of suffering unintended consequences from the physiologic changes that drugs are designed to effect.

Although there is good reason to believe that markers of vulnerability in older persons are associated with increased risk of ADRs, there is limited evidence about the nature of this relationship. A handful of studies have assessed one or two geriatric conditions among a broad range of potential predictors of ADRs, yet very little has been done to systematically evaluate the relationship between geriatric conditions and adverse reactions (4,15,16,17). In this study, we sought to test the association between geriatric conditions and ADRs using data on 808 vulnerable elderly outpatients from the VA Geriatric Evaluation and Management (GEM) Drug Study.

Methods

Participants

The VA GEM Drug study enrolled 808 patients aged 65 years and older admitted to medical or surgical wards at 11 VA medical centers (18). To meet inclusion criteria, patients were required to have at least 2 of 10 characteristics that identified them as vulnerable, including disability in at least one ADL, mild to moderate dementia (defined as diagnosis of dementia and Clinical Dementia Rating score of 0.5–2.0), incontinence, fall within the past 3 months, needing assistance with ambulation, malnourishment (defined as admission serum albumin <3.5 g/dL or weight less than 80% ideal body weight), depression (defined as preexisting diagnosis or new diagnosis established at screening), prolonged bed rest in the 2 weeks prior to hospital admission, an unplanned admission within 3 months of a prior hospital admission, and cerebrovascular accident within the past 30 days with residual neurologic deficits (19). This information was assessed through a combination of patient assessment (such as the Clinical Dementia Rating scale for dementia) and self-report by the patient or their proxy. In the underlying GEM study, participants were randomized in a 2 × 2 factorial design to a GEM intervention versus usual care as an inpatient and to a GEM clinic versus usual outpatient care upon discharge from the hospital. Participants were followed for 12 months following discharge from the index hospital stay.

Outcome Measures

Potential ADRs were identified using several methods (20). At the end of the follow-up period, patient charts were screened for evidence of potential ADRs, with particular attention paid to tracer events including use of narrow therapeutic index drugs, use of other high-risk drugs, changes in medications, adverse tracking reports, and ADRs diagnosed in the clinical chart. In addition, at the 12-month closeout interview, participants were asked if they had experienced an ADR during the past year, with further information collected if the patient answered affirmatively. A nurse and clinical pharmacists performed the chart and interview screening and prepared a narrative based on the FDA Medwatch form (21).

Blinded geriatrician and geriatric pharmacist pairs evaluated ADR causality using the narrative and the Naranjo algorithm, a validated method for determining the causality of potential ADRs that agrees well with expert clinician assessments of ADRs (agreement 86%–95%, $\kappa = 0.75$–0.91) (18,22). By convention, any event that was rated possible, probable, or definite by Naranjo scoring criteria was considered to be an ADR. In addition, raters used standardized criteria to classify ADRs by their severity and whether or not they were preventable (23,24). Disagreements between raters were resolved by consensus.

Our principal outcome measure was the number of ADRs of any type ("any ADRs") that occurred in the outpatient setting in the 12 months after discharge from the index hospitalization (18,25). Secondary outcome measures included the number of serious ADRs and the number of preventable ADRs during the same period. Serious ADRs were defined as those associated with death, hospitalization, permanent disability, or need for an intervention to prevent permanent impairment, whereas preventable ADRs were defined as ADRs resulting from errors in medication prescribing, monitoring, dispensing, or adherence. To evaluate the possibility that participants with higher geriatric burden might underreport ADRs, we also categorized all ADRs by the presence or absence of objective means of confirmation using a question from the Naranjo scale ("was the adverse event confirmed by any objective evidence?", coded as "yes" or "no, or do not know").

Primary Independent Variables

Our main predictor variables of interest were geriatric conditions, including geriatric syndromes and other "geriatric" features commonly found in older adults. These predictors included disability in at least one ADL, mild to moderate dementia, incontinence, recent fall, needing assistance with ambulation, malnourishment, depression, and prolonged bed rest. Each of these were assessed at the time of study enrollment and defined using the enrollment criteria described earlier. We approached these conditions in two ways. First, we evaluated each condition individually. Second, we created

a score to reflect the cumulative burden of these geriatric conditions, with each condition present contributing one point to the total score. For clarity of presentation, we term this the "geriatric burden score." This approach loosely follows the deficit accumulation principle articulated by Rockwood in which frailty is understood and measured as the sum of diverse deficits without attempting to assign weights to deficits in proportion to their presumed importance (26,27).

Other Covariates

To account for potential confounders of the relationship between geriatric conditions and ADRs, we reviewed the medical literature and previous work by Hanlon and colleagues for established and putative predictors of ADRs and identified variables in the GEM Drug Study data set that corresponded to these predictors and were assessed during hospitalization and the peri-discharge period (25). Based on this process, we included a variety of variables in our analyses, including demographic and socioeconomic characteristics (patient age, educational attainment, and marital status), measures of medication use (number of medications at hospital discharge, number of medications added during the index hospital stay, use of warfarin, benzodiazepines, sedative/hypnotics, nonaspirin nonsteroidal antiinflammatory drugs, and tricyclic antidepressants, and ability to use medications independently), ADR history (ADR during the index hospital stay), and comorbid medical and psychiatric burden and health services utilization (Charlson comorbidity score, Short Form-36 mental health subscore, and unplanned admission within 3 months of a prior admission). Of note, we did not include patient sex in our models due to limited power (98% of participants were men) nor did we include race due to little a priori evidence that race is associated with ADR risk (2,3,4,5,28,29).

Analyses

Descriptive statistics were calculated for all outcome measures, primary independent variables, and control variables. We conducted bivariate analyses using Poisson regression to determine the association between each of our predictor variables and our principal outcome measure (number of ADRs during the follow-up period) and our secondary outcome measures (preventable and serious ADRs). We tested for collinearity of predictor variables and found none that would require modifying or excluding one or more of these variables in our multivariable analyses.

Our multivariable analyses using Poisson regression proceeded as follows. First, we entered all variables except the geriatric burden score into a multivariable model. The geriatric burden score was excluded from this model because it was derived from the eight geriatric conditions included in the model and thus by definition is perfectly collinear with them. Next, we removed these eight individual geriatric conditions from the model and substituted in the single variable representing the geriatric burden score. Of note, each of these models controlled for study group assignment (both inpatient and outpatient), although we do not present results from this variable in the tables (because these are control variables and not of principal interest to our research question). To test for a possible impact of study group assignment on the association between vulnerability and ADR risk, we added two interaction terms (for the inpatient and outpatient treatment arms) to our main bivariate and multivariable analyses. These interaction terms were not statistically significant ($p > .20$ for all analyses) and thus were not included in our final models.

We repeated our analyses using two secondary outcomes: serious ADRs and preventable ADRs. Because of the smaller number of serious and preventable ADR outcomes, to preserve statistical power and prevent overfitting we took a slightly different approach than our analyses of any ADRs. In this modified approach, for each secondary outcome we restricted the multivariable model to exclude covariates with $p > .10$ on bivariate analysis. Based on a priori decisions, for each secondary outcome we also forced age, Charlson comorbidity score, and change in number of medications during the index hospital stay into the multivariable model (ie, we included them in the multivariable models regardless of results from the bivariate analyses).

Finally, we used generalized estimating equations to evaluate whether the level of geriatric burden was associated with the presence or absence of objective evidence to confirm the ADR (as defined earlier using an item from the Naranjo scale). These analyses were adjusted for intraparticipant correlation.

SAS Version 9.2 (SAS Institute, Cary, NC) was utilized to conduct all analyses. This research was approved by the institutional review boards at Duke University, the University of California San Francisco, and the Durham and San Francisco VA Medical Centers.

Results

Characteristics of participants are shown in Table 1. The mean age of participants was 74 years, and the great majority were men. Participants used multiple medications (mean of 8.7 medications at hospital discharge) and had substantial comorbid and geriatric burden, with each of eight geriatric conditions present in 8%–87% of participants. The number of medications used did not vary between participants with different levels of geriatric burden ($p = .48$; Figure 1).

ADRs were common during the 12-month follow-up period (Table 2). A total of 497 ADRs occurred in 269 patients (33% of the sample). One hundred and forty-one patients (17%) had one ADR, 70 (9%) had two ADRs, and 58 (7%) had three or more ADRs. Approximately one quarter of ADRs were considered serious (127/497; 26%), and 187 ADRs (38%) were considered preventable.

Table 1. Characteristics of Participants and Medication Use (N = 808 participants)

Characteristic	N (%) or Mean (SD)
Geriatric conditions	
Geriatric burden score*	2.9 ± 1.2
≥1 ADL dependencies	686 (85%)
Dementia	83 (10%)
Incontinence	212 (26%)
Falls	179 (22%)
Difficulty ambulating	705 (87%)
Malnourished	269 (33%)
Depressed	68 (8%)
Prolonged best rest	132 (16%)
Demographic characteristics	
Age (years)	74 ± 6
Male sex	788 (98%)
Did not graduate high school	438 (54%)
Race	
White	587 (73%)
African-American	193 (24%)
Other	28 (3%)
Married	442 (55%)
Medications/medication use	
# of medications at hospital discharge	8.7 ± 4.2
# of medications added during index inpatient stay†	−1.5 ± 3.6
Medications present at discharge	
Warfarin	118 (15%)
Benzodiazepines	87 (11%)
Sedative/hypnotics	16 (2%)
NSAIDs	114 (14%)
Tricyclic antidepressants	52 (6%)
Able to use medications independently	585 (72%)
History of ADRs	
ADR during index hospital stay	153 (19%)
Comorbid burden, mental health, and health services utilization	
Charlson comorbidity score	2.5 ± 1.9
SF36—mental health subscale raw score (out of 100)	65 ± 24
Unplanned admission within 3 months of prior admission	255 (32%)

Notes: ADL = activity of daily living; ADR = adverse drug reaction; NSAID = nonaspirin nonsteroidal antiinflammatory drug.

*Calculated as the number of geriatric conditions per patient, with possible scores ranging from 0 to 8.

†Calculated as total number of medications present at end of period minus total number of medications at beginning of period.

Three quarters of ADRs (365/497; 74%) had objective evidence that supported the presence of the ADR. ADRs that occurred in participants with higher levels of geriatric burden were more likely to be supported by objective evidence than those in participants with lower levels of geriatric burden (odds ratio = 1.32, 95% confidence interval [CI] = 1.03–1.69 for each additional point on the geriatric burden score). In addition, objective confirmation was more common in serious ADRs than in milder ones, with objective confirmation in 34% (25/73) of minor ADRs, 73% (216/297) of moderate ADRs, and 98% (124/127) of severe ADRs ($p < .001$).

The relationship between geriatric conditions and any ADRs is shown in Table 3. On bivariate analyses, the presence of one or more ADL dependencies was associated with lower rates of ADRs (incidence rate ratio [IRR] = 0.66, 95% CI = 0.53–0.81). Similarly, cumulative geriatric burden was negatively associated with ADRs, with each additional geriatric condition associated with an 8% lower incidence rate for ADRs (IRR = 0.92 per additional point, 95% CI = 0.85–0.99). Results for ADLs were similar after multivariable adjustment, with dependency in one or more ADLs remaining protective against ADRs (IRR = 0.78, 95% CI = 0.62–1.00; $p = .049$). However, on multivariable analysis that excluded the eight individual geriatric conditions, the geriatric burden score was not significantly associated with ADR risk (IRR = 0.95 per additional point, 95% CI = 0.88–1.04).

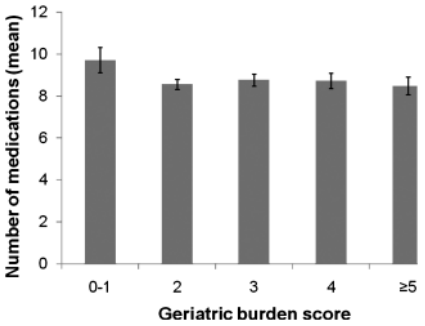

Figure 1. Number of medications used by subjects with different geriatric burden scores. "Number of medications" refers to number of medications used at hospital discharge. There was no significant association between geriatric burden score and number of medications used ($P = .48$ on trend analysis).

Several markers of medication use were strongly associated with ADR risk in both bivariate and multivariable analyses. Most notably, the strongest predictors of ADR risk were number of medications prescribed at hospital discharge (IRR = 1.05 per each additional medication, 95% CI = 1.03–1.08) and use of warfarin (IRR = 1.61, 95% CI = 1.30–2.00).

Table 4 shows the bivariate and multivariable analyses of geriatric conditions and serious and preventable ADRs. A history of recent falls was independently associated with future development of serious ADRs (IRR = 1.49, 95% CI = 1.00–2.21). No other geriatric condition was independently associated with the development of serious ADRs or preventable ADRs. Similarly, the geriatric burden score was not associated with increased risk of serious ADRs (multivariate

Table 2. Frequency and Characteristics of Adverse Drug Reactions (N = 497 ADRs)

Characteristic	n (%)
Severity of ADR	
Minor	73 (15)
Moderate	297 (60)
Severe	127 (26)
Preventable	187 (38)
How ADR was identified*	
Chart review only	409 (87)
Patient self-report only	33 (7)
Both chart review and patient self-report	34 (7)

Notes: ADR = adverse drug reaction.

*Source not available for 21 ADRs.

Table 3. Predictors of Adverse Drug Reactions of Any Type

Characteristic	Bivariate Analyses, IRR (95% CI)	Multivariable Analyses, IRR (95% CI)
Geriatric conditions		
≥1 ADL dependencies	0.66 (0.53–0.81)†	0.78 (0.62–1.00)*
Dementia	1.01 (0.76–1.36)	1.22 (0.88–1.68)
Incontinence	0.89 (0.72–1.01)	1.02 (0.81–1.27)
Falls	1.05 (0.85–1.30)	1.06 (0.85–1.31)
Difficulty ambulating	0.82 (0.64–1.04)	0.83 (0.63–1.09)
Malnourished	0.86 (0.70–1.04)	0.85 (0.69–1.04)
Depressed	1.12 (0.82–1.51)	1.01 (0.73–1.40)
Prolonged best rest	1.10 (0.87–1.39)	1.01 (0.79–1.28)
Demographics		
Age	1.00 (0.98–1.01)	1.00 (0.98–1.01)
Years of education	1.00 (0.97–1.02)	1.00 (0.97–1.02)
Marital status	1.14 (0.95–1.36)	1.09 (0.90–1.31)
Medications		
# of medications at hospital discharge	1.07 (1.05–1.09)†	1.05 (1.03–1.08)†
# of medications added during index inpatient stay	1.04 (1.01–1.06)†	1.01 (0.98–1.03)
Medications present at discharge		
Warfarin	1.69 (1.37–2.08)†	1.61 (1.30–2.00)†
Benzodiazepines	1.64 (1.29–2.07)†	1.16 (0.89–1.50)
Sedative/hypnotics	0.19 (0.05–0.75)*	0.14 (0.04–0.58)†
NSAIDs	1.29 (1.02–1.62)*	1.22 (0.96–1.55)
Tricyclic antidepressants	1.46 (1.07–1.99)*	1.26 (0.92–1.74)
Able to use medications independently	1.06 (0.86–1.29)	1.07 (0.86–1.34)
History of ADRs		
ADR during index hospital stay	1.10 (0.89–1.38)	1.04 (0.83–1.31)
Comorbid burden, mental health, and health services utilization		
Charlson comorbidity score	1.02 (0.98–1.07)	1.00 (0.95–1.05)
Short Form-36—mental health subscale raw score	1.00 (0.99–1.00)	1.00 (0.99–1.00)
Unplanned admission within 3 months of prior admission	1.59 (1.33–1.91)†	1.41 (1.16–1.71)†

Notes: ADL = activity of daily living; ADR = adverse drug reaction; CI = confidence interval; IRR = incidence rate ratio; NSAID = nonaspirin nonsteroidal anti-inflammatory drug.

*$p < .05$; †$p < .01$.

IRR = 1.07 per additional point, 95% CI = 0.92–1.24) or preventable ADRs (multivariate IRR = 1.05 per additional point, 95% CI = 0.93–1.20). Warfarin use was the only covariate consistently associated with an increased risk of any, serious, or preventable ADRs.

To evaluate the possibility that our results were negatively confounded by underreporting of ADRs in participants with extensive geriatric burden, we repeated our main analyses including only ADRs that were supported by objective evidence. We observed no significant association between geriatric burden score and ADR rates for all ADRs, serious ADRs, or preventable ADRs ($p > .15$ for each).

Discussion

In this study of 808 elderly patients, contrary to our hypothesis, we observed few positive associations between individual geriatric conditions or cumulative geriatric burden and risk of ADRs. In contrast, ADRs were observed less often in patients with at least one dependency in ADLs than in those who were fully independent in their ADLs. Results were generally similar when our analyses were restricted to preventable and serious ADRs, although a history of recent falls was positively associated with future development of the latter outcome.

Few studies have closely evaluated the association between geriatric conditions and risk of ADRs, but other research in outpatient and inpatient settings is generally consistent with our findings. In a small methodologically limited study of hospitalized older adults, von Renteln-Kruse and colleagues described higher rates of ADRs in patients with urinary incontinence and poor nutrition (although only bivariate analyses were presented) (15). In contrast, four higher quality studies identified no association between ADR risk and degree of mobility impairment (4) or independence in ADLs (1,16,17). Results of studies that evaluated cognitive impairment as a risk factor for ADRs have produced seemingly contradictory results, with two studies finding that worse cognitive function was associated with lower risk of ADRs (30,31) and three others finding no effect or associations in the oppose direction (1,17,32). These contradictory results may in part be explained by the complex interactions observed in these studies, with the association between cognitive impairment and ADR risk varying substantially by the type of medications used and recent introduction of new medications (30,31). Thus, although subtlety is required in interpreting these findings, the overall gist of the existing literature demonstrates little evidence of a clear and convincingly positive impact of geriatric conditions on ADR risk.

Table 4. Predictors of Serious and Preventable ADRs

Characteristic	Serious		Preventable	
	Bivariate Analyses, IRR (95% CI)	Multivariable Analyses, IRR (95% CI)	Bivariate Analyses, IRR (95% CI)	Multivariable Analyses, IRR (95% CI)
Geriatric conditions				
≥1 ADL dependencies	0.60 (0.40–0.90)*	0.74 (0.46–1.19)	0.83 (0.57–1.20)	1.00 (0.65–1.50)
Dementia	1.02 (0.68–1.52)	1.30 (0.75–2.26)	0.79 (0.47–1.34)	0.84 (0.48–1.48)
Incontinence	1.02 (0.68–1.52)	1.00 (0.64–1.53)	1.07 (0.78–1.49)	1.28 (0.90–1.82)
Falls	1.62 (1.11–2.36)*	1.49 (1.00–2.21)*	1.12 (0.80–1.57)	1.19 (0.83–1.69)
Difficulty ambulating	0.96 (0.57–1.59)	1.11 (0.63–1.95)	1.10 (0.71–1.72)	1.05 (0.65–1.71)
Malnourished	1.26 (0.88–1.80)	1.07 (0.73–1.57)	0.76 (0.55–1.05)	0.75 (0.54–1.06)
Depressed	0.74 (0.36–1.50)	0.65 (0.31–1.35)	1.24 (0.77–1.99)	1.16 (0.70–1.93)
Prolonged bed rest	1.39 (0.90–2.14)	1.19 (0.76–1.87)	1.38 (0.96–1.97)	1.18 (0.81–1.71)
Demographics				
Age	1.04 (1.01–1.07)*	1.04 (1.01–1.08)*	1.00 (0.98–1.03)	1.01 (0.99–1.04)
Years of education	1.04 (0.99–1.10)	1.05 (1.00–1.11)	0.98 (0.94–1.03)	—
Marital status	1.11 (0.78–1.58)	—	0.97 (0.73–1.29)	—
Medications				
# of medications at hospital discharge	1.07 (1.03–1.11)†	1.04 (0.99–1.09)	1.11 (1.07–1.14)†	1.07 (1.03–1.11)†
# of medications added during index inpatient stay	1.02 (0.97–1.07)	1.01 (0.95–1.06)	1.06 (1.02–1.10)†	1.01 (0.97–1.06)
Medications present at discharge				
Warfarin	2.05 (1.39–3.04)†	2.02 (1.34–3.04)†	1.68 (1.19–2.36)†	1.66 (1.17–2.35)†
Benzodiazepines	0.71 (0.37–1.35)	—	1.84 (1.27–2.67)†	1.15 (0.77–1.74)
Sedative/hypnotics	—	—	0.25 (0.03–1.78)	—
NSAIDs	0.50 (0.26–0.96)*	0.50 (0.26–0.96)*	1.61 (1.13–2.28)†	1.44 (1.00–2.08)
Tricyclic antidepressants	1.72 (0.97–3.05)	1.53 (0.84–2.80)	1.51 (0.92–2.48)	—
Able to use medications independently	0.71 (0.49 1.02)	0.79 (0.53–1.19)	0.92 (0.67–1.26)	—
History of ADRs				
ADR during index hospital stay	1.85 (1.26–2.71)†	1.75 (1.17–2.61)†	0.96 (0.66–1.40)	—
Comorbid burden, mental health, and health services utilization				
Charlson comorbidity score	1.18 (1.09–1.28)†	1.11 (1.01–1.21)*	1.03 (0.96–1.11)	1.00 (0.93–1.09)
Short Form-36—mental health subscale raw score	1.00 (0.99–1.01)	—	0.99 (0.99–1.00)*	1.00 (0.99–1.00)
Unplanned admission within 3 months of prior admission	1.46 (1.02–2.09)*	1.39 (0.94–2.03)	1.92 (1.44–2.56)†	1.75 (1.28–2.39)†

Notes: ADL = activity of daily living; ADR = adverse drug reaction; CI = confidence interval; IRR = incidence rate ratio; NSAID = nonaspirin nonsteroidal anti-inflammatory drug.

Variables with $p \geq .10$ on bivariate analyses were excluded from the multivariable models except for variables of a priori interest that were forced into these models. The model could not generate reliable estimates for sedative-hypnotic use for the outcome of serious ADRs.

*$p < .05$; †$p < .01$.

One potential explanation for our results—and those of other studies evaluating risk factors for ADRs—is that older adults with greater degrees of geriatric burden might be less likely to report ADRs. If present, this bias would negatively confound the observed association between geriatric conditions and ADR risk.

For example, in explaining their finding of a negative association between cognitive impairment and ADR risk, Onder and colleagues postulated that ADRs may be more difficult to detect in cognitively impaired adults due to underreporting of symptoms in this group, reduced physician attention to patients with dementia, and given the frequently heavy burden of comorbidity in patients with dementia, greater difficulty distinguishing an ADR from an underlying disease process (31).

We are unaware of any prior research that has directly evaluated differences in patient's self-report or physician's vigilance toward identifying ADRs in patients with versus without various geriatric conditions. Although we could not measure this directly, we did find that ADRs in elders with greater levels of geriatric burden were more likely to be accompanied by objective evidence. The relative paucity of ADRs without objective evidence in this group suggests that elders with higher geriatric burden may underreport subjective symptoms or otherwise present greater challenges in diagnosing ADRs that lack objective evidence to confirm the diagnosis. However, several features of our study reduce the risk that such potential bias in reporting had a substantial impact on our results. First, we found no association between geriatric burden and ADR rates after excluding ADRs that lacked objective confirmatory evidence. In addition, only 7% of ADRs were identified exclusively by self-report, with the remaining 93% identified wholly or in part through chart review. Although chart evidence of ADRs in part relies on the patient reporting their symptoms to clinicians, in other instances, clinical signs, laboratory tests, and directed

physician questioning can be used to detect ADRs without patient prompting (33,34). Finally, findings from the parent trial that outpatient GEM reduces the rate of serious ADRs compared with usual care demonstrates that differences in ADR risk between groups of patients can be identified using the methodologies employed in this study (18).

Many physicians are reluctant to prescribe medications to such people out of fear that these patients are at disproportionately high risk of developing adverse events. Such instincts are appropriate because vulnerable elders often suffer from substantial burden of comorbid illnesses and are commonly prescribed multiple medications, which both can increase risk of ADRs (2,3,4,5,28,29). However, our results suggest that specific geriatric conditions are not themselves positively associated with ADR risk. Thus, if a patient's comorbid illnesses and medication burden do not contraindicate adding additional medications, the presence of the geriatric conditions we studied should not necessarily dissuade the provider from prescribing potentially beneficial therapy.

We have no clear explanation for the finding that ADL dependency is associated with lower risk of ADRs. This observation may be spurious given its borderline significance and the relatively large number of predictors we studied, which increases the risk of false-positive results. In addition, the vulnerable nature of participants in the study may create a floor effect, whereby even those without ADL dependency had other characteristics that put them at risk. We are thus reluctant to conclude that ADL dependency is truly protective against ADRs, but we feel more confident in concluding that ADL dependency does not appear to substantially increase risk of these events.

Several limitations of our study merit discussion. First, as noted above, we cannot rule out the possibility that ADRs were detected differently in patients with greater or lesser degrees of geriatric burden, potentially biasing our results. Second, all participants had a minimum degree of vulnerability, operationalized by the study designers to encompass a wide range of potential problems ranging from specific geriatric syndromes to recent hospitalization or stroke (19). Thus, our results should not be construed as comparing healthy versus vulnerable elders but as comparing the association between ADR risk and geriatric conditions among patients who all had a baseline degree of vulnerability. It is possible that more pronounced associations would be observed in comparing healthy versus vulnerable elders. Third, our major predictors of interest were largely assessed by self-report, which may differ from physician diagnoses of these features. However, most of these features are typically diagnosed by physicians based on patient reports (eg, incontinence, falls). Fourth, our measure of cumulative geriatric burden has not been independently validated, and the scoring system (1 point for each problem) fails to account for the severity of each condition or its expected contribution to ADR risk. However, a similar accumulation-of-deficits approach (albeit more comprehensive) has been validated extensively by Rockwood and colleagues and may represent a fair approximation of the degree of geriatric burden that a clinician may perceive in daily office-based encounters with patients (27). Finally, because study patients were being discharged from the hospital at study baseline, it is uncertain how our results generalize to ambulatory participants without recent hospitalization.

In summary, we observed no positive association between a variety of geriatric conditions and risk of developing an ADR. Patients with such features often have a substantial degree of comorbid illnesses and multiple medication use, and it is prudent to exercise special caution in prescribing to such patients. Nevertheless, our findings suggest that prescribers need not be overly timid in prescribing medications that are truly appropriate to vulnerable older patients on account of geriatric conditions they might have.

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Conflict of Interest

None of the authors have financial conflicts of interest with the topics discussed in this manuscript.

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