Published in final edited form as:
J Am Geriatr Soc. 2011 April ; 59(4): 615–621. doi:10.1111/j.1532-5415.2011.03331.x.

Geriatric Conditions, Medication Use, and Risk of Adverse Drug Events in a Predominantly Male, Older Veteran Population

Michael A. Steinman, MD, **Brian C. Lund, PharmD**, **Yinghui Miao, MPH**, **W. John Boscardin, PhD**, and **Peter J. Kaboli, MD**
San Francisco VA Medical Center and Division of Geriatrics (MAS, YM, WJB) and the Department of Epidemiology and Biostatistics (WJB), University of California, San Francisco; and The Center for Research in the Implementation of Innovative Strategies in Practice (CRIISP) at the Iowa City VA Medical Center, Iowa City, IA (PJK, BCL); and the Division of General Internal Medicine, Department of Internal Medicine, University of Iowa (PJK); and the Department of Epidemiology, University of Iowa College of Public Health (BCL).

Abstract

Background—To determine whether geriatric conditions and functional impairment are independent risk factors for adverse drug events (ADEs).

Design—Prospective cohort study.

Setting and Participants—377 veterans from a Veterans Affairs medical center age 65 years or older and taking 5 or more medications.

Measurements—Geriatric conditions and functional status were assessed using patient interviews and structured assessments at study baseline. ADEs were elicited during patient interviews at 3 and 12 months after study enrollment using validated methods.

Results—The strong majority (97%) of participants were male, mean age was 74 +/− 5 years, and 123 (33%) had one or more dependencies in instrumental activities of daily living (IADLs). Over the one-year study period, 126 patients (33%) developed 167 ADEs. On multivariable analysis, risk of ADEs was not associated with any of the geriatric conditions we had sufficient power to evaluate, including IADL function, cognitive impairment, depression, visual impairment, incontinence, constipation, and a summative measure of geriatric burden comprising the above and history of falls or gait instability. In exploratory analyses, the strongest factor associated with ADES was the number of drugs added to a patient's medication regimen during the 1 year study period (incidence rate ratio 1.11 per each added drug, 95% CI 1.03–1.19).

Corresponding author: Michael Steinman, MD, 4150 Clement St, Box 181G, San Francisco VA Medical Center, San Francisco, CA 94121, mike.steinman@ucsf.edu, (tel) 415.221.4810 x3677, (fax) 415.750.6641. **Alternate corresponding author:** Peter Kaboli, MD, 601 Highway 6 West, Iowa City VA Medical Center, Iowa City, IA 52246, peter.kaboli@va.gov, (tel): 319.338-0581 x 7716.

Presentation: This work was presented at the annual meeting of the American Geriatrics Society, Orlando, May 2010

Conflicts of interest: The authors have no financial conflicts of interest with topics discussed in this manuscript (see full conflict of interest form on following page)

Author contributions:
Study concept and design: Steinman, Kaboli
Acquisition of subjects and/or data: Lund, Kaboli
Analysis and interpretation of data: Steinman, Lund, Boscardin, Miao, Kaboli
Preparation and critical review of manuscript: Steinman, Lund, Boscardin, Miao, Kaboli

Sponsor's role: None of the sponsors had any role in the study design, methods, analyses, and interpretation, or in preparation of the manuscript and the decision to submit it for publication.

Other disclosure: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

Conclusion—Common geriatric conditions and IADL function were not associated with ADEs in a predominantly male, older veteran population. While it is important to consider the unique circumstances of each patient, excessive caution in prescribing to elders with these geriatric conditions may not be warranted.

Keywords

drug therapy/adverse effects; frail elderly; polypharmacy

INTRODUCTION

Among older adults, functional impairment and geriatric syndromes such as falls and cognitive impairment provide valuable prognostic information, as older patients with such "geriatric" conditions have worse outcomes than matched controls. [1–4] Based on the vulnerability that these conditions confer, many clinicians exercise extra caution in prescribing to such patients on the assumption that they are at greater risk of suffering adverse drug events and other problems associated with medication use.

These concerns are supported by the conceptual basis for understanding frailty, which is distinct from but often co-occurs with geriatric syndromes and functional deficits. Frailty reflects decreased ability to respond to threats to homeostasis due to impairment of underlying physiologic and/or cognitive reserve. [5] For example, patients with impaired regulation of vascular tone may develop orthostatic signs or symptoms when given antihypertensive medications due to their inability to compensate to the physiologic changes these drugs induce. [6] To the extent that conditions commonly recognized as "geriatric" serve as markers of vulnerability, there is theoretical reason to believe that patients with such conditions are at increased risk of adverse drug events (ADEs).

Despite this theory and its implications for clinical practice, few studies have systematically evaluated these associations. In a small study, von Renteln-Kruse found that malnutrition and incontinence were positively associated with risk of ADEs on unadjusted analyses.[7] In contrast, a handful of studies have found no association between ADEs and dependency in activities of daily living, mobility limitations, or falls, and data on the association between cognitive function and ADEs is highly conflicting. [8–14] Thus, limited evidence calls into question the expected association between function, geriatric syndromes, and ADEs, but is insufficient to answer this question due to limitations of study design and focus.

To address this gap in knowledge, we used data from a study of ambulatory older veterans to evaluate whether common geriatric conditions were associated with risk of ADEs. Consistent with the theoretical model, we hypothesized that geriatric conditions would be positively associated with ADE risk.

METHODS

Data source

We used data from the Enhanced Pharmacy Outpatient Clinic study, a randomized trial of veterans age 65 and older in primary care clinics of the Iowa City VA Medical Center who were taking 5 or more medications. Subjects were randomized to usual care vs. a pharmacist clinic intervention that identified medication problems and communicated recommendations to the patient's primary care physician.

All subjects underwent a comprehensive interview and structured assessments at baseline to evaluate current medication use, medication-related problems (including ADEs), clinical

diagnoses, cognitive and functional status, and other parameters. Follow-up interviews about medication use and medication-related problems were conducted at 3 and 12 months. We included only subjects who had assessments of past medical history at baseline and medication information and ADE interviews completed at all study time points.

Measures

Our primary dependent variable was ADEs. Potential ADEs were identified during interviews with patients at 3 and 12 months by asking the validated question of whether the participant had "noticed any side effects, unwanted reactions, or other problems from medications" since the last study visit.[15] Family members were allowed to sit in on these interviews. If the patient reported problems, additional information was obtained about the event(s), the medication(s) of concern, and patient and provider responses. Each potential ADE was evaluated by a clinical pharmacist who was blinded to treatment assignment and to the hypothesis of the present research and who reviewed the medical record for additional evidence about the event. Using clinical judgment in consultation with standard drug information references, the pharmacist adjudicated the plausibility of the event being an ADE and identified the responsible medication(s).[16] ADEs that occurred during hospital stays were not considered. The principal investigator classified ADEs as significant, serious, or life-threatening using a published taxonomy. Examples of "significant" ADEs observed in the cohort include diarrhea, malaise, and sedation, whereas examples of "serious" ADEs include hypotension and agitation resulting in a fall. [17–18]

We assessed potential predictors of ADEs in 6 domains, including demographic characteristics, medication use, self-rated health, function, geriatric conditions, and other comorbid conditions.

Medication use—At study baseline, medication lists were compiled by consulting the computerized pharmacy profile in the electronic medical record and confirming medications with the patient, including use of over-the-counter medications, vitamins, supplements, and herbal remedies not included in the electronic pharmacy profile. In our analyses, we evaluated 3 markers of medication use, including (1) use of medications previously identified as conveying elevated risk of ADEs, including glucose-lowering drugs, loop diuretics, digoxin, anticonvulsants, warfarin, benzodiazepines, and drugs included in the Beers criteria (a consensus list of drugs to avoid in elders); (2) the total number of these high-risk drugs used; and (3) the total number of all medications taken by the patient.[19–22] In exploratory analyses, we also evaluated the addition of new drugs to the medication list between the baseline and 12 month interviews, which we assessed by counting the number of medications that were present on the reconciled medication list at 12 months that had not been present on the baseline medication list. This a priori analysis was informed by the observation that ADEs to a given drug are often more likely to occur shortly after the drug is started than after years of stable use.

Self-rated health—We assessed self-rated health at study baseline using a single item indicator on a scale of 0–100. Self-rated health has been demonstrated to predict important clinical outcomes independent of measures of disease-specific burden.[23]

Function—Using structured interviews, we evaluated independence in 7 instrumental activities of daily living (IADL) including using the telephone, using public transportation or driving, shopping, preparing meals, light housework, using medications, and handling finances. Each IADL was graded as requiring no help (0 points), some help (1 point), or full assistance (2 points). Data on more basic activities of daily living such as bathing, eating, and toileting were not available in the research dataset.

Geriatric conditions—Using a team of 4 study personnel (including a study physician, study pharmacist, and 2 student pharmacists extensively trained by members of the study team), we conducted comprehensive review of each patient's clinical chart at study baseline. This review examined problem lists and progress notes over a one-year look-back period to assess the presence of six conditions common in older adults, which for clarity of presentation we term "geriatric conditions." These conditions comprise a mix of classically-recognized geriatric syndromes and other diagnoses that, while typically lacking the multifactorial nature of geriatric syndromes, are common with advancing age and have been associated with worse health outcomes and physical and social functioning in older adults. [24–26] These conditions included (1) cognitive impairment (including diagnoses of dementia, cognitive impairment, and mental status changes); (2) depression; (3) visual impairment (including blindness, macular degeneration, cataracts, and glaucoma); (4) incontinence (including diagnoses of urinary retention and urgency and bladder dysfunction); (5) constipation; and (6) gait instability or falls. To improve our detection of cognitive impairment, we combined the chart review with results of the Short Portable Mental Status Questionnaire (SPMSQ) into a composite measure of cognitive impairment, defined as chart diagnosis of cognitive impairment or an education-normalized result of 2 or more errors on the SPMSQ. (SPSMQ scores were missing for 6 subjects, so we used the Multiple Imputation with Chained Equations procedure to impute test results for these patients). Only conditions which were active were coded as present (e.g., a past history of visual impairment that was corrected by cataract surgery would not be included).

To help evaluate the cumulative effect of recognizably geriatric conditions, we created a summary "geriatric burden score" that assigned 1 point to each geriatric condition present, plus 1 point for mild and 2 points for moderate to severe dependence in IADLs. While not a measure of frailty *per se*, this sum score approach broadly replicates a frailty index approach developed and validated by Rockwood and colleagues in which various patient conditions contribute to an additive score without attempting to weight each condition by the degree to which it related to overall patient health.[27–28]

Other clinical conditions—Based on chart diagnoses, we evaluated for the presence of heart failure and chronic renal insufficiency, each of which have been implicated as potentially important risk factors for ADEs. [14, 29] Similarly, we counted the total number of comorbid conditions present that were identified on chart review as a measure of overall comorbid burden.[30]

Analyses

We used Poisson regression to model the relationship between our predictors and ADEs. Consistent with this statistical technique, we present our results as incidence rate ratios, defined as the average number of ADEs in patients with the characteristic divided by the average number of ADEs in patients without the characteristic. To preserve power in our multivariable models, we excluded covariates that were prevalent in 5% or fewer of subjects and showed little association with ADEs on bivariate analyses (P>.20).

In our first model, we included all core predictors except the geriatric burden score and the total number of high-risk medications taken. (Because the geriatric burden score is derived from the geriatric conditions and IADL dependencies included in the model, it is perfectly collinear with them. Similarly, the number of high-risk medications taken is collinear with the specific high-risk drugs evaluated). We then repeated these analyses to include the geriatric burden score and number of high-risk mediations, while excluding the individual geriatric conditions, IADL variables, and high-risk medications that were used to define these summative measures. The parameter estimates for other covariates we evaluated did

not meaningfully vary between the models. All analyses also controlled for study group (in all analyses this covariate was not statistically significant, with P>.20).

Next, to evaluate the association between adding new medications and ADE risk, we added a variable that represents the number of medications that were present at the 12-month follow-up visit but not at the baseline visit. We cannot distinguish whether the ADEs we observed occurred before or after these medications were added, complicating interpretations of causality. Thus, this analysis should be viewed as exploratory.

We conducted several sensitivity analyses, including: 1) excluding the six patients with imputed data on cognitive function, and 2) including variables that were excluded from multivariable analyses to preserve statistical power. In all cases, results did not substantively change, so we report only the main findings. All analyses were conducted using Stata 10.0 (StataCorp, College Station, TX). This study was approved by the Research and Development Committee at the San Francisco and Iowa City VA Medical Centers and by institutional review boards at the University of California, San Francisco and the University of Iowa.

RESULTS

Among 377 study subjects, the mean age was 74 years, and the overwhelming majority were male and white (Table 1). The median number of medications used at baseline was 12 (interquartile range [IQR], 10–16). At the 12-month follow-up visit, patients were taking a median of 2 (IQR, 1–4) new drugs which had not been present at baseline. One-third of patients had some impairment in instrumental activities of daily living, and 43% had one or more geriatric conditions, the most common of which were cognitive impairment (15%), depression (14%), and visual impairment (12%).

Over the 12-month followup period, 126 patients suffered a total of 167 ADEs. Among the 167 ADEs, 153 (92%) were considered significant, 12 (7%) were serious or life-threatening, and 2 (1%) were not rated for severity. Fifty percent (83 of 167) of ADEs were caused by drugs which were present at the baseline assessment, with the other half (84 of 167) caused by drugs that were added after baseline.

Table 2 shows associations between geriatric conditions and ADEs after controlling for a variety of potentially confounding factors. None of the geriatric conditions we studied were significantly associated with risk of ADEs. Similarly, there was no association between ADE risk and a cumulative index of “geriatric burden” comprising the sum of geriatric conditions and IADL impairments. Results were similar in a sensitivity analysis that excluded IADL impairments from the geriatric burden index, with a P value of 0.81 for association between the revised index and ADE risk. The only factor significantly associated with ADE risk was use of glucose-lowering drugs, which was associated with a lower risk of ADEs.

We conducted an exploratory analysis to evaluate the association between ADE risk and the addition of new medications during the follow-up period that were present at the 12-month interview. After controlling for other covariates listed in Table 2, there was a positive association between use of new medications and ADE risk (IRR 1.11 per each additional medication, 95% CI 1.03–1.19). Addition of this covariate to our multivariable model did not meaningfully change the associations observed for the other variables. Similarly, we observed no significant interaction between the geriatric burden score and use of new medications in predicting risk of ADEs (P for interaction 0.69).

DISCUSSION

In this study of 377 older, predominantly male veterans, we found no association between the presence of various geriatric conditions such as IADL impairment, incontinence, and cognitive impairment and adverse drug events. These findings contradicted our hypothesis that geriatric conditions would result in a greater frequency of ADEs. However, in exploratory analyses we found that the use of new medications (present at the 12-month followup interview) was associated with a higher risk of ADEs in this older population.

We lack definitive proof about how to interpret the absence of an association between geriatric conditions and ADEs, but several possible explanations merit consideration. First, it is possible that the assumptions on which our hypothesis was founded are incorrect. We postulated that many drugs have the potential to cause ADEs by upsetting the homeostasis of physiologic systems on which they act, and that the decreased ability of frail elders to compensate for these challenges to homeostasis would result in clinically significant adverse events.[5] However, we evaluated common conditions that are often used clinically to mark a patient as “geriatric” rather than directly measuring the related but distinct construct of frailty.[5, 31] Moreover, even if the conditions we evaluated did serve as markers of impaired physiologic reserve, such deficits may only be important in situations where a patient’s impairments match a drug’s actions. For example, giving an antihypertensive agent to a patient with impaired vascular tone may result in orthostatic hypotension and falls, but may confer no increased risk of ADEs in patients with globally depressed physiologic reserve but no specific deficit in vascular tone.

It is also possible that our results were confounded by differences in ADE ascertainment between patients with and without geriatric conditions in our study. Although several studies have found that older patients are often more likely to identify ADEs than their physicians when queried on the topic, these events are often not reported.[32–34] Moreover, patients with markers of frailty are more likely to attribute disabilities to “old age” than their more robust peers, which may lead to disproportionate underreporting of both drug- and disease-associated symptoms in the most vulnerable patients.[35] Similarly, symptoms of ADEs are often misdiagnosed as markers of a disease process rather than as a drug reaction, and it is possible that patients with geriatric conditions are more likely to be misdiagnosed.[36] In addition, ADEs are often difficult to ascertain definitively in the research setting, and our use of a single reviewer to adjudicate ADEs could lead to misclassification with potential to bias our results.

Another potential source of negative confounding could be different prescribing patterns for patients with and without the geriatric conditions of interest – for example, if frail patients received more conservative treatment regimens than non-frail patients, their risk of ADEs would be reduced. However, we were largely able to account for differences in medication use by controlling for the numbers of medications taken and for use of 7 different types of high-risk medications. Finally, our power to detect associations between geriatric conditions and ADEs was also limited by the relative paucity of major geriatric conditions in our cohort, with some conditions being present in only a small subset of the patients studied. These low prevalence rates likely reflect under-detection, since many geriatric conditions are poorly documented in the clinical chart. To increase our power to identify differences, we selected relatively liberal thresholds to define patients as having a condition of interest. For example, most patients classified as having cognitive impairment received this designation by virtue of errors on the Short Portable Mental Status Questionnaire (SPMSQ) rather than a clinical diagnosis of dementia, and the range of these errors suggested only mild problems with cognitive functioning. Thus, in many cases we compared patients without geriatric conditions to patients with relatively mild presentations of these conditions.

It remains uncertain to what extend our findings would be duplicated in another sample with more validated and precise measures of the geriatric conditions that were the focus of our study.

While several factors had the potential to bias our results toward a negative result, our predominant finding that geriatric characteristics were not associated with ADE risk is supported by a limited body of related research. As noted earlier, previous studies conducted in a mix of clinical settings found no independent association between dependency in activities of daily living, degree of mobility limitations, or falls and risk of ADEs.[8–10, 14] In addition, studies of the relationship between cognitive impairment and ADEs have produced contradictory results. Research on hospitalized older adults and on recipients of home health care found significantly lower rates of ADEs in patients with higher degrees of cognitive impairment,[11–12] while other studies in hospital and dementia clinic settings found no effect or the opposite result (i.e., ADE rates increased as cognitive function worsened).[9, 13–14] The authors of these studies noted that these puzzling results may in part be explained by a complex web of interactions. For example, Onder *et al*. found that while all-cause ADEs were significantly less common in patients with worse cognitive function, ADEs from neuropsychiatric drugs occurred significantly more frequently in these patients.[12] Similarly, Gray *et al* observed a positive association between Mini-Mental Status Exam scores and ADEs in hospitalized older adults, but the opposite effect when considering only patients who had new medications added during their hospital stay.[11]

In addition to our focus on geriatric conditions, a secondary area of interest was exploratory analyses to assess how changes in medication use over time may impact ADEs. We found that addition of new medications over the study period (as defined by the presence of medications at the 12-month followup interview which had not been present at baseline) had a stronger association with ADEs than any other variable assessed, even after controlling for baseline number of medications and types of medications used. Because changes in medication use occurred over the same period that potential ADEs were assessed, this association should be interpreted with caution. (For example, it is possible that some patients were started on a new medication to replace a drug that was present at baseline but which was subsequently discontinued due to an adverse reaction). However, the concept of evaluating ADE risk in relation to changes in medication use is an important area of future study. For most drugs, ADEs are most likely to emerge shortly after a drug is started, so the presence of multiple recent medication starts represents a high-risk time for ADEs.[8, 37] Our data support this contention. Half of ADEs were caused by drugs which had been started during the one-year study period, even though the median number of new drugs present at the end-of-study assessment (2) was far less than the median number of drugs used at baseline (12). Serial cross-sectional evaluations of medication use do not completely capture all changes made to a medication regimen, for example short courses of antibiotics or drugs stopped shortly after initiation due to side effects. Nonetheless, our data suggest that the proportion of recently-started drugs that result in ADEs is substantially higher than the proportion of drugs present at baseline that result in ADEs.

While the meaning of our findings may be viewed through different lenses, the absence of an association between geriatric conditions and ADE risk has important implications for clinical care. Clinicians are often hesitant to prescribe medications to elders with geriatric syndromes or functional deficits for fear that such patients are at disproportionate risk of being harmed by drug therapy. These concerns are appropriate. Vulnerable elders often suffer from multiple comorbidities and take multiple medications, each of which has been identified as a risk factor for ADEs, thus meriting a judicious approach to prescribing in patients with these risk factors.[22, 38–39] Moreover, patients with underlying vulnerabilities in specific physiologic systems and functional abilities appear more likely to suffer harm when

challenged with drugs known to cause side effects in those domains.[6, 12] However, in the absence of a global association between geriatric conditions and ADE risk, it may not be necessary for physicians to exercise excessive caution in prescribing to older patients solely on the basis of their having geriatric conditions. Where there is a strong clinical indication, older adults with geriatric conditions may have the opportunity to benefit from drug therapy without being at disproportionate risk of being harmed.

Acknowledgments

Funding: Supported by the National Institute on Aging and the American Federation for Aging Research (1K23-AG030999); and by the Health Services Research and Development Service, Department of Veterans Affairs through an investigator-initiated research award (SAF98–152); Research Career Development award (RCD 03-033-1); and the Center for Research in the Implementation of Innovative Strategies in Practice (CRIISP) (HFP 04–149) at the Iowa City VA Medical Center (Drs. Kaboli and Lund)

REFERENCES

1. Carey EC, Covinsky KE, Lui LY, et al. Prediction of mortality in community-living frail elderly people with long-term care needs. J Am Geriatr Soc. 2008; 56:68–75. [PubMed: 18031487]
2. Tinetti ME, Kumar C. The patient who falls: "It's always a trade-off". JAMA. 2010; 303:258–266. [PubMed: 20085954]
3. Mehta KM, Yaffe K, Langa KM, et al. Additive effects of cognitive function and depressive symptoms on mortality in elderly community-living adults. J Gerontol A Biol Sci Med Sci. 2003; 58:M461–M467. [PubMed: 12730257]
4. Holroyd-Leduc JM, Straus SE. Management of urinary incontinence in women: scientific review. JAMA. 2004; 291:986–995. [PubMed: 14982915]
5. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci. 2004; 59:255–263. [PubMed: 15031310]
6. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: Diagnosis and treatment. Am J Med. 2007; 120:841–847. [PubMed: 17904451]
7. von Renteln-Kruse W, Thiesemann N, Thiesemann R, et al. Does frality predispose to adverse drug reactions in older patients? Age Ageing. 2000; 29:461–462. [PubMed: 11108427]
8. Forster AJ, Clark HD, Menard A, et al. Adverse events among medical patients after discharge from hospital. CMAJ. 2004; 170:345–349. [PubMed: 14757670]
9. Gray SL, Sager M, Lestico MR, et al. Adverse drug events in hospitalized elderly. J Gerontol A Biol Sci Med Sci. 1998; 53:M59–M63. [PubMed: 9467435]
10. Chrischilles E, Rubenstein L, Van Gilder R, et al. Risk factors for adverse drug events in older adults with mobility limitations in the community setting. J Am Geriatr Soc. 2007; 55:29–34. [PubMed: 17233682]
11. Gray SL, Mahoney JE, Blough DK. Adverse drug events in elderly patients receiving home health services following hospital discharge. Ann Pharmacother. 1999; 33:1147–1153. [PubMed: 10573310]
12. Onder G, Gambassi G, Scales CJ, et al. Adverse drug reactions and cognitive function among hospitalized older adults. Eur J Clin Pharmacol. 2002; 58:371–377. [PubMed: 12185561]
13. Ganjavi H, Herrmann N, Rochon PA, et al. Adverse drug events in cognitively impaired elderly patients. Dement Geriatr Cogn Disord. 2007; 23:395–400. [PubMed: 17396031]
14. Onder G, Petrovic M, Tangiisuran B, et al. Development and validation of a score to assess risk of adverse drug reactions among in-hospital patients 65 years or older: The GerontoNet ADR risk score. Arch Intern Med. 2010; 170:1142–1148. [PubMed: 20625022]
15. Chrischilles EA, Foley DJ, Wallace RB, et al. Use of medications by persons 65 and over: data from the established populations for epidemiologic studies of the elderly. J Gerontol. 1992; 47:M137–M144. [PubMed: 1512428]

16. Lund BC, Carnahan RM, Egge JA, et al. Inappropriate prescribing predicts adverse drug events in older adults. Ann Pharmacother. 2010; 44:957–963. [PubMed: 20460558]
17. Folli HL, Poole RL, Benitz WE. Medication error prevention by clinical pharmacists in two children's hospitals. Pediatrics. 1987; 79:718–722. [PubMed: 3575028]
18. Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group. JAMA. 1997; 277:307–311. [PubMed: 9002493]
19. Budnitz DS, Shehab N, Kegler SR, et al. Medication use leading to emergency department visits for adverse drug events in older adults. Ann Intern Med. 2007; 147:755–765. [PubMed: 18056659]
20. Chrischilles EA, VanGilder R, Wright K, et al. Inappropriate medication use as a risk factor for self-reported adverse drug effects in older adults. J Am Geriatr Soc. 2009; 57:1000–1006. [PubMed: 19507293]
21. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med. 2009; 169:1952–1960. [PubMed: 19933955]
22. Field TS, Gurwitz JH, Harrold LR, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. J Am Geriatr Soc. 2004; 52:1349–1354. [PubMed: 15271125]
23. Lee SJ, Moody-Ayers SY, Landefeld CS, et al. The relationship between self-rated health and mortality in older black and white Americans. J Am Geriatr Soc. 2007; 55:1624–1629. [PubMed: 17697102]
24. Yaffe K, Edwards ER, Covinsky KE, et al. Depressive symptoms and risk of mortality in frail, community-living elderly persons. Am J Geriatr Psychiatry. 2003; 11:561–567. [PubMed: 14506090]
25. Unutzer J. Clinical practice. Late-life depression. N Engl J Med. 2007; 357:2269–2276. [PubMed: 18046030]
26. Rosenberg EA, Sperazza LC. The visually impaired patient. Am Fam Phys. 2008; 77:1431–1436.
27. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci. 2007; 62:722–727. [PubMed: 17634318]
28. Hastings SN, Purser JL, Johnson KS, et al. Frailty predicts some but not all adverse outcomes in older adults discharged from the emergency department. J Am Geriatr Soc. 2008; 56:1651–1657. [PubMed: 18691282]
29. Corsonello A, Pedone C, Corica F, et al. Concealed renal insufficiency and adverse drug reactions in elderly hospitalized patients. Arch Intern Med. 2005; 165:790–795. [PubMed: 15824299]
30. Klabunde CN, Warren JL, Legler JM. Assessing comorbidity using claims data: An overview. Med Care. 2002; 40(8 Suppl):IV-26–IV-35.
31. Saliba D, Elliott M, Rubenstein LZ, et al. The Vulnerable Elders Survey: A tool for identifying vulnerable older people in the community. J Am Geriatr Soc. 2001; 49:1691–1699. [PubMed: 11844005]
32. Blenkinsopp A, Wilkie P, Wang M, et al. Patient reporting of suspected adverse drug reactions: A review of published literature and international experience. Br J Clin Pharmacol. 2007; 63:148–156. [PubMed: 17274788]
33. Weingart SN, Gandhi TK, Seger AC, et al. Patient-reported medication symptoms in primary care. Arch Intern Med. 2005; 165:234–240. [PubMed: 15668373]
34. Mannesse CK, Derkx FH, de Ridder MA, et al. Do older hospital patients recognize adverse drug reactions? Age Ageing. 2000; 29:79–81. [PubMed: 10690701]
35. Sarkisian CA, Liu H, Ensrud KE, et al. Correlates of attributing new disability to old age. Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc. 2001; 49:134–141. [PubMed: 11207866]
36. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: The prescribing cascade. BMJ. 1997; 315:1096–1099. [PubMed: 9366745]
37. Forster AJ, Murff HJ, Peterson JF, et al. Adverse drug events occurring following hospital discharge. J Gen Intern Med. 2005; 20:317–323. [PubMed: 15857487]
38. Hanlon JT, Schmader KE, Koronkowski MJ, et al. Adverse drug events in high risk older outpatients. J Am Geriatr Soc. 1997; 45:945–948. [PubMed: 9256846]

39. Green JL, Hawley JN, Rask KJ. Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? Am J Geriatr Pharmacother. 2007; 5:31–39. [PubMed: 17608245]

Table 1

Characteristics of subjects at baseline

Predictor	N (%)
Patient age, yr	
Mean ± SD	74.2 ± 5.5
Male sex	367 (97%)
Caucasian race	369 (98%)
Number of medications at baseline	
Median (Interquartile range)	12 (10, 16)
High-risk medications used at baseline	
Glucose-lowering drug	104 (28%)
Loop diuretic	104 (28%)
Digoxin	33 (9%)
Anticonvulsant	33 (9%)
Any Beers criteria drug	28 (7%)
Warfarin	18 (5%)
Benzodiazepine	19 (5%)
Number of high-risk medications at baseline ‡	
0	171 (45%)
1	120 (32%)
2 or more	86 (23%)
Number of new medications present at 12 month follow-up	2 (1, 4)
Median (Interquartile range)	
Self-reported health score	
Median (Interquartile range)	75 (50, 80)
IADL dependencies *	
Fully independent	254 (67%)
Mild dependence	73 (19%)
Moderate or severe dependence	50 (13%)
Geriatric conditions	
Cognitive impairment	54 (15%) †
Depression	54 (14%)
Visual impairment	47 (12%)
Incontinence	29 (8%)
Constipation	23 (6%)
Falls or gait instability	6 (2%)
Geriatric burden score *	

Predictor	N (%)
0 (no geriatric condition)	151 (40%)
1 (1 geriatric condition)	110 (30%)
≥ 2 (2 or more geriatric conditions)	110 (30%)
Other comorbid conditions	
Chronic renal insufficiency	32 (8%)
Heart failure	31 (8%)
Number of comorbid conditions	
Median (Interquartile range)	11 (8, 14)
Study group	
Control	175 (46%)
Intervention	202 (54%)

*Geriatric burden score calculated as one point for each geriatric condition present, plus 1 point for mild dependence in IADLs and 2 points for moderate dependence.

†N=371 for assessment of cognitive impairment

‡Not counting Beers criteria drugs (to prevent double-counting, since certain benzodiazepines and higher-dose digoxin prescriptions are counted as Beers criteria drugs).

Table 2

Association between geriatric conditions and other subject characteristics and adverse drug events

Predictor	Bivariate IRR (95% CI)	*P* Value	Multivariable IRR (95% CI)	*P* Value
Patient age	0.99 (0.96 – 1.02)	0.54	0.99 (0.96 – 1.02)	0.43
Male sex	1.11 (0.41 – 3.00)	0.84	†	
Non-white race	0.75 (0.19 – 3.03)	0.69	†	
Number of medications at baseline	1.03 (0.99 – 1.06)	0.09	1.03 (0.99 – 1.08)	0.16
High-risk medications used at baseline				
Glucose-lowering drug	0.65 (0.44 – 0.95)	0.03	0.61 (0.41 – 0.91)	0.02
Loop diuretic	1.25 (0.91 – 1.73)	0.17	1.20 (0.81 – 1.78)	0.37
Digoxin	1.10 (0.66 – 1.85)	0.71	1.06 (0.59 – 1.89)	0.86
Anticonvulsant	0.88 (0.50 – 1.55)	0.66	0.79 (0.44 – 1.43)	0.44
Any Beers criteria drug	0.96 (0.54 – 1.74)	0.91	0.95 (0.51 – 1.76)	0.86
Warfarin	0.87 (0.41 – 1.86)	0.72	†	
Benzodiazepine	0.70 (0.31 – 1.59)	0.40	†	
Number of high-risk medications at baseline ‡	0.94 (0.79 – 1.11)	0.45	0.84 (0.69 – 1.03) *	0.10
Self-reported health score ≥ 75	1.12 (0.81 – 1.54)	0.49	1.21 (0.86 – 1.70)	0.28
IADL dependencies (Ref: Fully independent)				
Mild dependence	1.18 (0.81 – 1.72)	0.80	1.25 (0.84 – 1.86)	0.95
Moderate or severe dependence	0.98 (0.61 – 1.56)		0.91 (0.54 – 1.54)	
Geriatric conditions				
Cognitive impairment	1.11 (0.73 – 1.68)	0.63	1.12 (0.72 – 1.72)	0.62
Depression	1.10 (0.73 – 1.68)	0.65	0.95 (0.60 – 1.49)	0.82
Visual impairment	0.69 (0.41 – 1.18)	0.18	0.69 (0.39 – 1.21)	0.19
Incontinence	1.18 (0.70 – 2.01)	0.53	1.01 (0.57 – 1.77)	0.98
Constipation	0.88 (0.45 – 1.72)	0.70	0.77 (0.38 – 1.55)	0.47
Fall or gait instability	1.91 (0.78 – 4.65)	0.15	1.91 (0.71 – 5.14)	0.20
Geriatric burden score* (Ref: 0)				
1	0.95 (0.68 – 1.33)	0.81	0.84 (0.58 – 1.21) *	0.79
2 or more	1.13 (0.70 – 1.81)		1.04 (0.63 – 1.73) *	
Other comorbid conditions				
Congestive heart failure	1.26 (0.77 – 2.09)	0.36	0.97 (0.50 – 1.87)	0.93
Chronic renal insufficiency	0.83 (0.46 – 1.50)	0.55	0.76 (0.41 – 1.40)	0.37
Number of comorbidities (Ref: < 10)				
10 – 13 comorbidities	1.14 (0.79 – 1.66)	0.37	1.17 (0.78 – 1.76)	0.57
≥ 14 comorbidities	1.18 (0.82 – 1.71)		1.14 (0.71 – 1.84)	

Predictor	Bivariate IRR (95% CI)	*P* Value	Multivariable IRR (95% CI)	*P* Value
Study group (intervention vs. control)	0.94 (0.70 – 1.28)	0.70	0.89 (0.64 – 1.23)	0.47

*Geriatric burden score is collinear with IADL dependencies and the geriatric conditions listed in the table, and the number of high-risk medications is collinear with the specific high-risk medications listed in the table. The multivariable parameter estimates for these summative variables are derived from separate models that excluded the collinear covariates. Results are combined into a single table for clarity of presentation.

†Male sex, non-white race, and use of warfarin and benzodiazepines were not included in the multivariable model to preserve statistical power for the remaining covariates (see methods).

‡Not counting Beers criteria drugs (to prevent double-counting, since certain benzodiazepines and higher-dose digoxin prescriptions are counted as Beers criteria drugs).