Potentially Inappropriate Medications and Functional Decline in Elderly Hospitalized Patients

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OBJECTIVES: To verify whether the use of potentially inappropriate medications (PIMs) is associated with loss of independence in elderly in-patients by promoting adverse drug reactions (ADRs).

DESIGN: Prospective observational study.

PARTICIPANTS: Five hundred six patients aged 65 and older admitted to 11 acute care medical wards.

MEASUREMENTS: In-hospital loss of one or more activities of daily living (ADLs) and three or more ADLs. PIMs were identified according to diagnosis-independent Beers criteria and ascertained by study physicians based on daily review of medical and nurse records. The relationship between risk factors and outcomes was assessed using logistic regression.

RESULTS: Overall, 104 patients (20.6%) were taking at least one PIM at the time of admission (baseline users), and 49 (9.7%) were newly prescribed at least one PIM during their hospital stay. The loss of one or more ADLs occurred in 9.6% of baseline users, 16.3% of new users, and 8.5% of nonusers (P = .21) and that of three or more ADLs in 7.7% of baseline users, 12.2% of new users, and 4.8% of nonusers (P = .10). The lack of association was confirmed after correction for potential confounders, including ADRs. The occurrence of ADRs was strongly associated with both outcomes (odds ratio (OR) = 7.80, 95% confidence interval (CI) = 3.53–17.3 for the loss of ≥1 ADLs; OR = 3.98, 95% CI = 1.50–10.5 for the loss of ≥3 ADLs), but PIMs caused only six of 106 ADRs.

CONCLUSIONS: ADRs to any drugs more than the use of PIMs might be associated with functional decline in elderly hospitalized patients, but because the power of this study was too limited to definitively exclude a direct relationship between PIMs and functional decline, this merits further investigation. J Am Geriatr Soc 2009.

Key words: potentially inappropriate medications; Beers criteria; functional decline; adverse drug reactions

Functional decline is frequent in elderly hospitalized patients, and the loss of physical function predicts worsening quality of life and increasing morbidity and mortality and has relevant social and economic implications. Older patients are particularly exposed to the risk of developing new functional deficits during hospitalization; thus, the identification of factors contributing to the development of functional decline during a hospital stay is a relevant goal in geriatric clinical practice. The use of potentially inappropriate medications (PIMs, i.e., of drugs with a particularly high risk of adverse drug reactions (ADRs) in frail hospitalized elderly people) might be among these factors. It has been demonstrated that in home-dwelling elderly subjects, chronic use of PIMs is associated with impaired physical performance and greater rate of hospitalization. Accordingly, limiting PIMs might be valuable not only from the perspective of preventing ADRs. Criteria identifying PIMs in elderly people were developed in 1991 for use in the elderly nursing home population and were subsequently expanded and made generalizable to the whole population aged 65 and older in 1997 and revised in 2002. Previous investigations reported on the extensive use of PIMs in older populations in various settings, with a prevalence ranging from 12% to 40%, but the clinical relevance of PIM
use in elderly in-patients has been assessed only with regard to outcomes such as in-hospital ADRs and mortality but not with regard to the risk of functional decline.\cite{14,15} The evidence pertaining to home-dwelling elderly people and the dramatic effect a hospital stay has on personal capabilities makes this outcome worthy of assessment in hospitalized elderly people.

It was hypothesized that inappropriate drug use is associated with greater risk of loss of personal independence in elderly hospitalized patients, and the objective of this study was to evaluate whether this relationship exists and, if so, whether a greater incidence of ADRs mediates it.

**METHODS**

**Patients**

The present study used data from a collaborative observational study group, the PharmacosurVeillance in the elderly Care, based in community and university hospitals located throughout Italy, aimed at surveying drug consumption, occurrence of adverse drug reactions, and quality of hospital care. The main objective of the study was to investigate the prevalence and correlates of potentially inappropriate prescribing in elderly hospitalized patients and to measure its effect on short-term and 1-year clinical outcomes.

All patients consecutively admitted to the participating wards (11 acute care medical wards and 3 long-term care and rehabilitation units) from April 1 to June 30, 2007, were asked to participate in the study. After obtaining written informed consent, a study physician with specific training completed a questionnaire for each patient at admission to the hospital and updated it daily. A training session was conducted at the coordinating center, and an instruction manual was delivered to each clinical center. In particular, the training covered all of the components of the assessment (see Data Recorded Included parts A–E, below), with special emphasis on how to detect ADRs (on the logical process underlying the interpretation of a new clinical event as a potential ADR). Researchers judged simulated clinical cases under the guidance of two senior researchers (CA, PC). The training lasted until the achievement of good interrater agreement in the identification and coding of ADRs and diagnoses.

**Data Recorded Included**

Part A—Demographic and pre-admission data: Age, sex, admission diagnosis, place of living information, marital status, years of education, number of hospital admission in the previous 12 months, family arrangement, alcohol consumption, smoking habits. For drugs taken before admission, patients were asked to display the drug containers and the physician’s instructions. For cognitively impaired patients, this information and those about adherence were checked through the patient’s relatives or caregivers.\cite{17} Drugs were coded according to Anatomical and Therapeutical Classification.\cite{18}

Part B—Socioeconomic status: Occupation before retiring, economic status, need of economic help for health problems, formal and informal assistance.

Part C—Clinical problems: Diagnoses and diagnostic procedures performed during stay coded by the trained physician using the International Classification of Disease, Ninth Revision, Clinical Modification.\cite{19} Information about destination at discharge and evolution of the main diagnosis was also collected. For drugs taken during the stay, to establish the duration of the therapy and which drugs were administered simultaneously during hospitalization, the starting and ending dates of therapy were recorded. If the dosage was modified, the name of drug, the new dosage, the initiation and discontinuation dates of the new dosage, and the main reasons that determined the modification of the therapy were also recorded.\cite{17} The list of drugs prescribed at discharge was also collected.\cite{17}

Part D—Comprehensive geriatric assessment: Mini Mental State Examination (MMSE),\cite{20} Geriatric Depression Scale (GDS),\cite{21} activities of daily living (ADLs) and instrumental ADLs,\cite{22,23,24} Cumulative Illness Rating Scale (CIRS),\cite{25} presence of pressure sores, urinary incontinence, fecal incontinence, use of urinary cathether, clinical history of falls, syncope, dizziness, blood pressure, heart rate, body temperature, weight, height, waist circumference, weight loss in the previous 3 months.

Part E—ADRs: An ADR was defined according to the World Health Organization definition, which refers to any noxious, unintended, and undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy. This definition excludes therapeutic failures, intentional and accidental poisoning (i.e., overdose), drug abuse, errors in drug administration, and nonadherence.\cite{26} The study physicians evaluated the participants on each day of their hospital stay for new potential ADRs. They were instructed to check the medical chart and new laboratory analyses and to ask the nurse, the attending physician, and the participants themselves for any new event, regardless of its apparent relation to the drugs prescribed. The decision as to whether to consider the new event an ADR was left to their judgment. For each suspected ADR, the study physician coded clinical description, severity, and eventual evolution. In addition, he collected detailed information about the drug(s) identified as the potential culprit. The attending physician rated the severity of each ADR as mild (the withdrawal of the suspected drug was not necessary), moderate (the withdrawal of the suspected drug was necessary, but the ADR was not life threatening), or severe (life-threatening ADR).\cite{17} The researcher was not aware of the analysis to be performed using the recorded data.

Part F—Laboratory parameters: Routine blood analyses performed at the time of admission and at discharge. Once discharged, patients were followed up every 3 months for 1 year.

Overall, 762 patients were screened in the survey period, but 72 (9.4%) refused to participate, leaving a final sample of 690. Twenty-five patients who died during hospital stay were excluded from the present study, as were patients enrolled in long-term care or rehabilitation units (n = 159), leaving a final sample of 506 patients for the analysis. The present study used only data collected from admission to discharge from the hospital. The Ethical Committee of the Italian National Research Center on Aging (INRCA) approved the study protocol.

**Analytical Approach**

The main outcome of the present study was the loss of physical independence in completing ADLs. Overall func-
tional capabilities were rated using a seven-item (transferring, ambulation, dressing, eating, toileting, bathing, and continence) ADL scale22,24 at admission and discharge. Performance on individual tasks was scored according to the five levels of difficulty recommended by the World Health Organization: without difficulty, with difficulty but without help, help for only part of the activity, help for total activity, and not able to perform.27 For each ADL item, needing help for total activity or being not able to perform it was considered to indicate loss of the explored function. To investigate the relationship between exposure to PIMs and different degrees of functional impairment, two different outcome variables were defined: loss of one or more ADLs and loss of three or more ADLs from admission to discharge.

PIMs were identified according to the diagnosis-independent 2003 revision of the Beers criteria.9 Patients who were already taking a PIM at admission (baseline users) and those who started a PIM during their hospital stay (new users) were separately analyzed.

Statistical Analysis
According to the basic hypothesis, the occurrence of any ADR during hospital stay was considered as a potential correlate of the outcomes. Based on the available literature, the following potential correlates were also considered: anthropometric and sociodemographic data (age, sex, body mass index, smoking habit, alcohol consumption), history of falls during the previous year and occurrence of falls during the hospital stay, health status indexes (level of personal independence in ADLs at admission, cognitive impairment as ascertained based on an age- and education-adjusted MMSE score < 24, and depressed mood (GDS score > 5)), selected comorbid conditions (diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, stroke or transient ischemic attack, chronic cerebrovascular disease, renal failure, and malignancies), and CIRS comorbidity and severity scores. The overall number of drugs, excluding PIMs, and the length of hospital stay were calculated and considered in the analysis.

First, the prevalence of the use of PIMs in the population studied was calculated, and baseline users of one or more PIMs and new users were compared with nonusers. Contingency tables with chi-square were used for categorical variables and one-way analysis of variance for continuous variables. Age, sex, and variables significantly distinguishing users from nonusers at P < .1 were entered into the multivariable logistic regression model to identify independent correlates of the outcomes. Functional status at admission was also considered as a potential confounder. The number of drugs used during the hospital stay excluding PIMs was also entered into the final multivariable models, given that polypharmacy is known to be associated with ADRs.28 The presence of collinearity between variables entered in the final regression model was excluded by assessing the effect of individual variables on the standard error of regression coefficients, as reported by Hosmer and Lemeshow.29 This analysis was repeated including the occurrence of any ADR during the hospital stay to verify whether ADRs could mediate the effects of PIMs on functional status. All drugs causing ADRs in the database were reviewed, and the relationship between increasing number or severity of ADRs and functional decline was investigated.

All statistical analyses were performed using SPSS software (version 10.0; SPSS Inc., Chicago, IL).

RESULTS
Overall, 104 of 506 patients (20.6%) were taking one or more PIMs at the time of admission, and 49 (9.7%) were newly prescribed one or more PIMs during their hospital stay. The prevalence of baseline and newly prescribed drugs listed in the Beers criteria is reported in Figure 1. Of them, the most frequently used at the baseline was ticlopidine, followed by doxazosin, amiodarone, and ferrous sulfate. The most frequently newly prescribed PIMs were ticlopidine, long-acting benzodiazepines, ferrous sulphate, and amiodarone.

Baseline users of PIMs were younger but had greater cumulative comorbidity and clinical severity scores and were more frequently affected by hypertension, stroke, and chronic cerebrovascular disease than nonusers. New users had a greater prevalence of depression and a lower prevalence of chronic obstructive pulmonary disease than nonusers. ADRs occurred in 14.4% of baseline users and in 16.3% of new users (Table 1). The loss of one or more ADLs occurred in 9.6% of baseline users, 16.3% of new users, and 8.5% of nonusers (P = .21), and that of three or more ADLs in 7.7% of baseline users, 12.2% of new users, and 4.8% of nonusers (P = .10).

In the logistic regression analysis, the use of PIMs was not independently associated with loss of one or more or three or more ADLs. After also adjusting for the occurrence of any ADR during the hospital stay, the association between baseline or new use of PIMs and functional decline continued to be nonsignificant (Table 2).

According to the fully adjusted model, the following variables qualified as independent correlates of the outcomes or were close to the threshold of significance: the occurrence of ADRs (odds ratio (OR) = 7.80, 95% CI = 3.53–17.3) for the loss of ≥1 ADLs; OR = 3.98, 95% CI = 1.50–10.5 for the loss of ≥3 ADLs), age (for each 1-year increase: OR = 1.11, 95% CI = 1.05–1.18 and OR = 1.11, 95% CI = 1.03–1.18, respectively), CIRS comorbidity score (OR = 1.21, 95% CI = 0.98–1.50 and OR = 1.23, 95% CI = 0.97–1.58, respectively), and number of drugs excluding PIMs (OR = 1.03, 95% CI = 0.99–1.11 and OR = 1.07, 95% CI = 0.99–1.15, respectively). Chronic cerebrovascular disease (OR = 2.82, 95% CI = 1.18–6.77) was significantly associated with the loss of one or more ADLs, whereas the number of lost ADLs at admission was negatively associated with the loss of three or more ADLs (OR = 0.76, 95% CI = 0.60–0.97).

Patients experiencing an ADR during their hospital stay were more likely to be female (72.4% vs 52.0%, P = .003) and cognitively impaired (62.1% vs 49.1%, P = .06), used a greater number of drugs (15.2 ± 7.9 vs 9.9 ± 4.8, P = .001), had greater overall comorbidity (CIRS comorbidity score 4.5 ± 1.8 vs 3.6 ± 1.9, P = .001), and more frequently had congestive heart failure (37.9% vs 20.3, P = .002) and renal failure (27.5% vs 14.5%,
Of the 58 patients experiencing one or more ADRs during their hospital stay, 29 had a single ADR, 17 had two ADRs, and 12 had three or more ADRs. The diagnosed ADR was judged to be moderate to severe in 22 of 58 patients (37.9%). The greater the severity of ADRs, the greater likelihood of experiencing a functional loss during the hospital stay, whereas having two or more ADRs was associated only with loss of three or more ADLs (Table 3).

When reviewing drugs causing ADRs in the database, it was found that only a minority of ADRs could be ascribed to the use of PIMs (Table 4).

**DISCUSSION**

This study shows that the use of PIMs, as ascertained based on Beers criteria, is not associated with decline in personal capabilities in elderly patients in acute care medical wards, even if the data suggest that some correlation might exist with the loss of three or more ADLs. Although, as expected, ADRs were strongly correlated with the outcome, drugs considered inappropriate caused few of them (6/106), indicating that the ADRs, more than PIMs, could be associated with loss of independence.

These data are in contrast with others showing an association between use of PIMs and disability. The most likely explanation for this discrepancy lies in the fact that those studies were cross-sectional, and some of the Beers drugs might simply be more frequently used in frail patients. In the current sample, for example, patients prescribed Beers drugs were more frequently affected by stroke and other cerebrovascular diseases. Furthermore, ticlopidine, the most used of the Beers drugs in this study, was usually prescribed to patients with a greater atherosclerotic burden; two or more cardio- or cerebrovascular conditions were found in 86.8% of ticlopidine users, versus 60.3% in non-users, \( P < .001 \). This further supports the possibility that,
in previous studies, Beers drugs might be associated with disability as a marker of an at-risk condition rather than being a risk factor. The strong association between ADRs and functional decline adds to the knowledge of the spectrum of ADR-related negative outcomes. Although ADRs might also be a marker of frailty, as suggested by the clinical profile of patients experiencing ADR in the current study, the analysis of individual ADRs suggests that more than one-third were judged moderate to severe (were severe enough to affect the level of personal independence). ADRs were the main correlate of severe functional decline in a logistic model corrected for the global number of drugs used and the use of Beers drugs. Furthermore, ADRs were frequently multiple (in 50% of the patients experiencing them) and important, such as gastrointestinal bleeding, respiratory failure, and delirium, thus, seeming severe enough to affect personal capabilities. Further supporting this view is the fact that disability and mortality share most of their predictors in different epidemiological models and clinical contexts.31–33 Accordingly, the repeatedly reported link

### Table 1. Sociodemographic and Clinical Characteristics of Patients According to the Use of One or More Potentially Inappropriate Medications (PIMs)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All N = 506</th>
<th>No Use of PIMs n = 353</th>
<th>Baseline Use of ≥1 PIMs n = 104</th>
<th>New Use of ≥1 PIMs n = 49</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>80.1 ± 6.0</td>
<td>80.4 ± 6.1</td>
<td>78.8 ± 5.2</td>
<td>80.6 ± 6.2</td>
<td>.04</td>
</tr>
<tr>
<td>Female, %</td>
<td>54.3</td>
<td>53.8</td>
<td>53.8</td>
<td>59.2</td>
<td>.77</td>
</tr>
<tr>
<td>Body mass index &lt; 20 kg/m², %</td>
<td>8.3</td>
<td>9.3</td>
<td>4.8</td>
<td>8.2</td>
<td>.34</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>5.3</td>
<td>5.4</td>
<td>3.8</td>
<td>8.2</td>
<td>.54</td>
</tr>
<tr>
<td>Alcohol consumption &gt; 0.5 L wine equivalent, %</td>
<td>2.8</td>
<td>2.8</td>
<td>2.9</td>
<td>2.0</td>
<td>.95</td>
</tr>
<tr>
<td>Number of lost activities of daily living at admission, mean ± SD</td>
<td>1.1 ± 2.3</td>
<td>1.2 ± 2.3</td>
<td>0.8 ± 1.8</td>
<td>1.5 ± 1.6</td>
<td>.10</td>
</tr>
<tr>
<td>Geriatric Depression Scale score &gt; 5, %</td>
<td>39.3</td>
<td>39.1</td>
<td>33.7</td>
<td>53.1</td>
<td>.07</td>
</tr>
<tr>
<td>Mini-Mental State Examination score ≤ 24, %</td>
<td>50.6</td>
<td>51.0</td>
<td>47.1</td>
<td>55.1</td>
<td>.63</td>
</tr>
<tr>
<td>Cumulative Illness Rating Scale score, mean ± SD</td>
<td>3.7 ± 1.9</td>
<td>3.5 ± 1.9</td>
<td>4.3 ± 2.0</td>
<td>3.5 ± 1.6</td>
<td>.001</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>1.8 ± 0.3</td>
<td>1.8 ± 0.3</td>
<td>1.9 ± 0.4</td>
<td>1.8 ± 0.3</td>
<td>.002</td>
</tr>
<tr>
<td>History of falls during the previous year, %</td>
<td>28.9</td>
<td>26.6</td>
<td>34.6</td>
<td>32.7</td>
<td>.24</td>
</tr>
<tr>
<td>Falls during stay, %</td>
<td>2.6</td>
<td>2.9</td>
<td>1.9</td>
<td>2.1</td>
<td>.85</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>25.7</td>
<td>23.8</td>
<td>31.7</td>
<td>26.5</td>
<td>.26</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>70.6</td>
<td>67.4</td>
<td>81.7</td>
<td>69.4</td>
<td>.02</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>29.4</td>
<td>28.9</td>
<td>34.6</td>
<td>22.4</td>
<td>.28</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>16.4</td>
<td>15.6</td>
<td>19.2</td>
<td>16.3</td>
<td>.68</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>22.3</td>
<td>22.7</td>
<td>24.0</td>
<td>24.0</td>
<td>.54</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, %</td>
<td>35.8</td>
<td>38.5</td>
<td>36.5</td>
<td>14.3</td>
<td>.004</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>23.7</td>
<td>24.4</td>
<td>25.0</td>
<td>16.3</td>
<td>.44</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack, %</td>
<td>13.0</td>
<td>10.8</td>
<td>20.2</td>
<td>14.3</td>
<td>.04</td>
</tr>
<tr>
<td>Cerebrovascular disease, %</td>
<td>13.8</td>
<td>11.6</td>
<td>19.2</td>
<td>18.4</td>
<td>.09</td>
</tr>
<tr>
<td>Renal failure, %</td>
<td>16.0</td>
<td>13.9</td>
<td>22.1</td>
<td>18.4</td>
<td>.12</td>
</tr>
<tr>
<td>Liver disease, %</td>
<td>0.8</td>
<td>0.6</td>
<td>1.0</td>
<td>2.0</td>
<td>.54</td>
</tr>
<tr>
<td>Malignancies, %</td>
<td>9.3</td>
<td>9.9</td>
<td>8.7</td>
<td>6.1</td>
<td>.67</td>
</tr>
<tr>
<td>Number of drugs during stay (excluding PIMs), mean ± SD</td>
<td>10.6 ± 5.5</td>
<td>10.4 ± 5.2</td>
<td>10.6 ± 5.5</td>
<td>12.0 ± 7.5</td>
<td>.15</td>
</tr>
<tr>
<td>Any adverse drug reaction during stay, %</td>
<td>11.5</td>
<td>9.9</td>
<td>14.4</td>
<td>16.3</td>
<td>.24</td>
</tr>
<tr>
<td>Length of stay, days, mean ± SD</td>
<td>11.8 ± 7.1</td>
<td>11.8 ± 7.3</td>
<td>10.9 ± 5.4</td>
<td>13.6 ± 8.3</td>
<td>.08</td>
</tr>
</tbody>
</table>

SD = standard deviation.

### Table 2. Relationship Between Use of Potentially Inappropriate Medications (PIMs) and Functional Decline According to Logistic Regression Summary

<table>
<thead>
<tr>
<th>Use of PIMs</th>
<th>Loss of ≥1 ADLs</th>
<th>Loss of ≥3 ADLs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds Ratio (95% Confidence Interval)</td>
<td>P-Value</td>
<td>Odds Ratio (95% Confidence Interval)</td>
</tr>
<tr>
<td>Nonusers</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Baseline users</td>
<td>1.10 (0.48–2.51)</td>
<td>.82</td>
</tr>
<tr>
<td>New users</td>
<td>1.51 (0.58–3.92)</td>
<td>.40</td>
</tr>
<tr>
<td>Additionally adjusted for occurrence of any adverse drug reaction during stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline users</td>
<td>1.06 (0.45–2.48)</td>
<td>.89</td>
</tr>
<tr>
<td>New users</td>
<td>1.43 (0.52–3.94)</td>
<td>.49</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, number of lost activities of daily living at admission, Geriatric Depression Scale score > 5, Cumulative Illness Rating Scale comorbidity score, hypertension, chronic obstructive pulmonary disease, stroke or transient ischemic attack, cerebrovascular disease, and number of drugs excluding PIMs.

ADL = activity of daily living.
between ADRs and mortality makes it reasonable that ADRs also mark frail patients at risk of disability. This has been proved in selected populations; ADRs such as hypoglycemia in people with diabetes mellitus or hypotension in populations with and without hypertension (e.g., patients with heart failure) are associated with accelerated functional decline. Moreover, ADRs are associated with longer stay, and longer stay, in turn, might per se carry a greater risk of functional decline, given that the acute care hospital frequently poses several barriers to mobility. Finally, ADRs are more common in patients with renal or liver impairment, which are important indicators of impaired homeostatic mechanisms. Renal dysfunction frequently remains unrecognized in elderly people and predicts the risk of developing ADRs to hydrosoluble drugs. Thus, several reasons support the hypothesis that ADRs might contribute to functional decline. Accordingly, prevention of in-hospital ADRs is expected to preserve personal capabilities. These findings seem robust, because a wide set of potential confounders was taken into account, and the study was a prospective one, although definitive proof of the relationship between ADRs and functional decline would require that interventions preventing ADRs also preserve personal capabilities.

The fact that 42 of 506 patients lost more than three ADL deserves consideration. Only a detailed analysis of individual case histories would allow disease-related functional decline to be distinguished from procedural-related functional decline. Among procedural-related disabilities should be considered those attributable to ADRs, inadequate or improper therapy, lack of nutritional support, and other factors suggesting a poor-quality process of care, although only one disease with a recognized disabling potential, chronic cerebrovascular disease, was among the independent correlates of the outcome, whereas ADRs (a procedural-related factor) emerged as the main correlate. This finding seems consistent with an important role of

<table>
<thead>
<tr>
<th>ADRs</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>11.1 (4.18–29.5) .001</td>
<td>2.73 (0.70–10.6) .15</td>
</tr>
<tr>
<td>2</td>
<td>4.30 (1.09–16.9) .04</td>
<td>2.97 (0.58–15.1) .19</td>
</tr>
<tr>
<td>≥3</td>
<td>6.20 (1.40–27.4) .02</td>
<td>9.63 (2.13–43.8) .003</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, number of lost activities of daily living at admission, Geriatric Depression Scale score > 5, Cumulative Illness Rating Scale comorbidity score, hypertension, chronic obstructive pulmonary disease, stroke or transient ischemic attack, cerebrovascular disease, number of drugs excluding potentially inappropriate medications (PIMs), and use of PIMs.

ADL = activity of daily living.

Table 3. Relationship Between Number or Severity of Adverse Drug Reactions (ADRs) and Functional Decline During Stay

Table 4. Summary of Beers Listed (Upper Panel) and All Other Drugs (Lower Panel) Causing Adverse Drug Reactions (ADRs) During Hospital Stay
procedural factors as potential determinants of functional decline of hospitalized elderly people. Previous reports about highly prevalent inadequate nutrition and hydration of elderly hospitalized patients are in keeping with this hypothesis.\textsuperscript{39,40} Furthermore, the positive effect of in-hospital comprehensive geriatric assessment and intervention programs\textsuperscript{41} and of strategies designed to prevent functional decline\textsuperscript{42} are consistent with a concurrent disabling role of practice-related modifiable factors. These findings and considerations might improperly depict the acute care hospital as a disabling setting. It is worthy to observe that 9.7\% of patients showed improvement in one or more ADLs, and 77.5\% had ADLs unchanged with regard to preadmission levels. Nevertheless, the risk of in-hospital functional decline increases markedly with age,\textsuperscript{3} and the results of the current study reinforce the message that clinicians should closely monitor the functional status of elderly hospitalized patients.

This study has several limitations. First, some proportion of patients who died might have experienced functional decline before dying. Thus it is likely that the analytical procedure underestimates the incidence of the outcome and the strength of its relationship with ADRs and Beers drugs, although it was judged that, an intermediate functional assessment lacking, using the composite outcome “death or disability” might have provided an unreliable estimate of true correlates of incident disability. Second, the Beers list of PIMs is questionable for several aspects.\textsuperscript{43,44} For instance, although amiodarone has limited effectiveness in maintaining sinus rhythm in older adults, together with greater risk of QT interval prolongation and torsades de pointes,\textsuperscript{9,45} it is among recommended drugs for the treatment of atrial fibrillation in patients with heart failure.\textsuperscript{45} Additionally, the Beers list does not address several other issues, such as duplicate drug class prescriptions, drug–drug interactions, inappropriate duration of therapy, and underuse of lifesaving drugs, such as warfarin to prevent cardioembolic events in patients with atrial fibrillation or beta-blockers in patients with coronary artery disease.\textsuperscript{46} Accordingly, Beers-listed PIMs refer to truly inappropriate medications only to some extent. Third, changes in functional status from admission to discharge were recorded; thus, some patients might have experienced functional decline before the onset of ADRs. Thus, it cannot be definitively concluded that the observed relationship between ADRs and functional decline was a causal one. Furthermore, the use of physician-reported ADRs probably underestimated the extent of ADRs. In addition, only one assessor assessed ADRs for the center, although based on the good interrater agreement achieved in the training session, it is likely that this is a minor limitation. Given the low incidence of ADRs to PIMs, the effect, if any, of ADRs to PIMs rather than that of ADRs as a whole on functional decline could not be assessed, although it should also be considered that PIMs may increase the generic risk of ADRs by interacting with other drugs not considered inappropriate.\textsuperscript{47} Finally, because of its limited power, this study may lack precision in estimates of the associations observed.

In conclusion, this study shows that ADRs more than PIMs, as codified by the Beers criteria, might be associated with functional decline in elderly patients admitted to acute care medical wards. Research on larger populations is needed to assess the respective role of individual ADRs and to verify to what extent ADRs mediate the reported disabling potential of selected diseases\textsuperscript{24,48} in the acute care setting. Furthermore, the present results suggest that disability should be included with mortality and length of stay among the potential consequences of ADRs for clinical and epidemiological purposes, as well as among the modifiable outcomes in programs designed to prevent ADRs in elderly in-patients.

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**REFERENCES**


