

Original Research

Potentially inappropriate prescribing and the risk of adverse drug reactions in critically ill older adults

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ABSTRACT*

Background: Potentially inappropriate medication (PIM) use in the elderly is associated with increased risk of adverse drug reactions (ADRs), but there is limited information regarding PIM use in the intensive care unit (ICU) setting.

Objective: The aim of the study is to describe the prevalence and factors associated with the use of PIM and the occurrence of PIM-related adverse reactions in the critically ill elderly.

Methods: This study enrolled all critically ill older adults (60 years or more) admitted to medical or cardiovascular ICUs between January and December 2013, in a large tertiary teaching hospital. For all patients, clinical pharmacists listed the medications given during the ICU stay and data on drugs were analyzed using 2012 Beers Criteria, to identify the prevalence of PIM. For each identified PIM the medical records were analyzed to evaluate factors associated with its use. The frequency of ADRs and, the causal relationship between PIM and the ADRs identified were also evaluated through review of medical records.

Results: According to 2012 Beers Criteria, 98.2% of elderly patients used at least one PIM (n=599), of which 24.8% were newly started in the ICUs. In 29.6% of PIMs, there was a clinical circumstance that justified their prescription. The number of PIMs was associated with ICU length of stay and total number of medications. There was at least one ADR identified in 17.8% of patients; more than 40% were attributed to PIM, but there was no statistical association.

Conclusions: There is a high prevalence of PIM used in acutely ill older people, but they do not seem to be the major cause of adverse drug reactions in this population. Although many PIMs had a clinical circumstance that led to their prescription during the course of ICU hospitalization, many were still present upon hospital discharge. Therefore, prescription of PIMs should be minimized to improve the safety of elderly patients.

Keywords: Drug-Related Side Effects and Adverse Reactions; Inappropriate Prescribing; Inpatients; Intensive Care Units; Aged; Brazil

INTRODUCTION

In recent years, drug-related illnesses have been an important concern in elderly care. Older people are more likely to experience adverse drug events than are young patients because of comorbidities, polypharmacy and age-related changes in the pharmacodynamics and pharmacokinetics of drugs.^{1,2}

Inappropriate prescribing of medications is a potential problem that has received significant attention in the medical literature as it relates to medication use in older adults and its role as a potential predictor of negative hospital outcomes.^{3,4} A potentially inappropriate medication (PIM) is defined as a drug in which the risks associated with prescribing it outweigh its potential benefits, particularly when safer alternatives exist.⁵ The Beers Criteria is among the most commonly used methods for assessing the appropriateness of prescribed drugs for older people in all clinical settings, and has been widely used for prescription profile studies, education and evaluation of costs.⁶

However, there is disagreement in the literature over the designation of certain drugs as inappropriate⁷, particularly in complex conditions of intensive care units (ICUs), where many PIMs are reasonable options.⁸ Most of the current literature evaluates PIM use among older people living in the community.^{9,10} Recently, PIM use has been studied in hospitalized non-ICU elderly patients^{4,11}, but there is limited information regarding PIM use in acutely ill older adults in the ICU setting. Thereby, the objectives of this study were to determine the prevalence and factors associated with the use of PIMs and identify the frequency of PIM-related adverse reactions (PIM-ADR) in critically ill older people.

METHODS

Study Design and Data Collection

This retrospective cross-sectional study was conducted in a large tertiary teaching hospital in the south of Brazil. All critically ill older people over the age of 60 who were admitted to medical or cardiovascular ICUs between January and December 2013 were enrolled in the study. The age cutoff of 60 was chosen according to the recommendations of the World Health Organization¹² for developing countries. Individuals were excluded from the study if their hospital stay was less than 24 hours. Patients admitted more

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than once to the ICUs during the study period were included as new subjects.

Clinical pharmacists with at least two years of experience performed all data collection and the determination of PIM and ADRs. In case of disagreement between the pharmacists during the classifications, a senior clinical pharmacist was consulted. Demographic, clinical and drug related use was collected from the hospital's computerized databases and analysis of medical records (including physician notes and medication administration records) using standardized forms. These data included information on patient age, gender, medical history, admission diagnoses, comorbidities and medication use.

The medications were analyzed in four distinct points: (1) before admission to the ICU (i.e., outpatient drugs registered at the time of hospital admission, when available, added to new drugs prescribed during hospitalization in general wards), (2) during the admission to the ICU (i.e., drugs that were continued after ICU admission and added to new drugs prescribed during ICU hospitalization), (3) discharge from ICU, and (4) hospital discharge. Data collection on the first point was performed only to know what PIMs were initiated for the first time to the patient during their stay in the ICU.

This study received approval from the local hospital research ethics committee (CEP/HC/UFPR: 644.579).

Determination of Potentially Inappropriate Medication

To establish the prevalence of PIMs at the hospital's ICUs, we considered all patients admitted to these units. PIMs were analyzed using 2012 Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.⁶ As there is no screening tool for the detections of PIMs developed in Brazil, the Beers criteria were chosen to identify PIMs due to their applicability to the Brazilian context. For the present study, we used the three categories of PIM (i.e., drugs to be avoided independent of diagnoses or conditions, drugs to be avoided considering disease or syndrome, and drugs to be used with caution in older adults). Doses were assessed when necessary. In addition, medical records were reviewed in order to identify factors described that motivated the prescription of a PIM and, based on this information we re-assessed appropriateness of each PIM prescribed.

Adverse Drug Reactions

To evaluate the occurrence of PIM-ADRs, a representative sample size was calculated from the population of patients who used at least one PIM during the ICU hospitalization period (i.e. 588 patients), allowing for a 5% maximum error and a 95% confidence level, and complete medical records were reviewed to identify possible ADRs. The calculated sample size (n=185) was randomly selected via systematic sampling from a mixed-gender list of older people admitted to the ICU and that made use of PIM.

Trained clinical pharmacists conducted a structured review of patients' medical records in order to identify ADRs and possible PIM-ADRs, using a standard institutional instrument adapted from Naranjo's algorithm to determine the causality of the ADR. This instrument considered three main criteria: (1) prior description in literature – Beers criteria and drug databases (Micromedex® Solutions and UpToDate®) – as a possible adverse sign or symptom, (2) temporality (temporal incidence of the ADR consistent with the use of the evaluated medicine), and (3) the description of alternative cases that could have caused the reaction (current clinical condition of the patient or another drug). A sign or symptom was only considered as an ADR if it fulfilled these three criteria.

Statistical Analysis

IBM SPSS Statistics 20 software was used to analyze the data. Quantitative variables were described by mean and standard deviation (SD) if the normality hypotheses (Kolmogorov-Smirnov test) were fulfilled, and by median and first and third quartiles (Q1, Q3) otherwise. Qualitative variables were described by frequency and percentage. Correlation between variables was performed using Spearman's test for nonparametric data.

Bivariate analysis was conducted for selection of variables that can influence the use of PIM, based on previous published studies. Age, sex, number of

Table 1. Demographic and clinical characteristics of critically ill elderly patients (n=599)

Characteristic	Value
Male, n (%)	329 (54.9)
Age, median (IQR)	71 (65–77)
Age range, years, n (%)	60–95
	60–74 393 (65.6)
	75–84 166 (27.7)
	≥ 85 40 (6.7)
Number of comorbidities, median (IQR)	2 (1–4)
Number of drugs, median (IQR)	11 (9–14)
Intensive care unit type at admission, n (%)	
	Medical 408 (68)
	Cardiology 191 (32)
Admission diagnosis, n (%)	
	Cardiogenic shock, myocardial infarction, congestive heart failure 106 (17.7)
	Sepsis or acute respiratory distress syndrome 88 (14.7)
	Surgery 82 (13.7)
	Acute upper gastrointestinal bleeding 42 (7.0)
	Acute respiratory distress syndrome without infection 29 (4.8)
	Other 252 (42.1)
Hospital length of stay, days, median (IQR)	14 (7–28)
ICU length of stay, days, median (IQR)	5 (3–10)
Hospital admission service, n (%)	
	General ward 344 (57.4)
	ICU 255 (42.6)
Discharging service, n (%)	
	Medical 192 (32.0)
	Surgical 85 (14.2)
	Other 322 (53.8)
>1 hospitalizations in 2013, n (%)	131 (26.4)
Mortality, n (%)	168 (28)
IQR, interquartile range	

Table 2. Potentially inappropriate medications identified by 2012 Beers Criteria (n=1864)

Type of medication	Number of drugs (%)	
Drugs to be avoided independent of diagnoses or conditions		
Anticholinergics (excludes TCAs)		
Dexchlorpheniramine	24	(1.3)
Diphenhydramine	13	(0.7)
Promethazine	21	(1.1)
Antispasmodics - scopolamine	36	(1.9)
Cardiovascular		
Alpha1 blockers – doxazosin	3	(0.2)
Alpha agonists		
Clonidine	28	(1.5)
Metildopa	14	(0.8)
Antiarrhythmic drugs – amiodarone	145	(7.8)
Digoxin > 0.125 mg/day	34	(1.8)
Nifedipine	7	(0.4)
Spironolactone > 25 mg/day	64	(3.4)
Central Nervous System		
Tertiary TCAs		
Amitriptyline	28	(1.5)
Clomipramine	1	(0.1)
Antipsychotics - first and second generation	155	(8.3)
Barbiturates - phenobarbital	13	(0.7)
Benzodiazepines	156	(8.4)
Endocrine		
Insulin, sliding scale	131	(7.0)
Gastrointestinal		
Metoclopramide	534	(28.6)
Mineral oil	125	(6.7)
Pain medications		
Non-COX-selective NSAIDs, oral	22	(1.2)
Drugs to be avoided considering disease or syndrome		
In heart failure		
diltiazem	1	(0.1)
In delirium		
H2-receptor antagonist	3	(0.2)
corticosteroids	4	(0.2)
benzodiazepines	3	(0.2)
TCAs	1	(0.1)
In dementia and cognitive impairment		
antipsychotics	2	(0.1)
anticholinergic	1	(0.1)
H2 antagonists	1	(0.1)
benzodiazepines	1	(0.1)
History of falls or fractures		
TCAs	1	(0.1)
benzodiazepines	2	(0.1)
In Parkinson's disease		
metoclopramide	1	(0.1)
Drugs to be used with caution in older adults		
Aspirin for primary prevention of cardiac events in adults ≥ 80 years old	7	(2.4)
Carbamazepine	10	(3.5)
SSRIs	26	(9.0)
Vasodilators	246	(85.1)
TCAs, tricyclic antidepressants; COX, cyclooxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors		

comorbidities, days of delirium, total number of drugs, hospital and ICU length of stay were included in the model. A multiple linear regression model was conducted to include all variables that were significantly associated with the number of PIMs in the bivariate analysis. The dependent variable was the use of at least one PIM by an older adult in the ICU. The presence of independent errors between the covariates was assessed using the Durbin-Watson test. Collinearity diagnosis was made by the inflation factor of variance, and collinear variables were excluded from the model. Results were expressed by the coefficient of determination (R^2)

and the beta value with a confidence interval. A p value <0.05 was considered statistically significant.

RESULTS

Data were obtained from 599 admissions of 486 older adults, of whom 131 (26.4%) had more than one hospitalization in 2013. The median age of participants was 71 years (IQR 65–77), and 54.9% were male. The main characteristics of the study population are shown in Table 1.

Table 3. Selected examples of clinical circumstances described in the medical records that motivated the prescription of potentially inappropriate medications during hospitalization in intensive care units
• Use of amiodarone for the restoration of sinus rhythm in critically ill patients with hemodynamically unstable atrial fibrillation and to control the ventricular response in patients with atrial fibrillation and rapid ventricular response.
• Use of haloperidol to control agitation or psychotic symptoms in the patient with delirium.
• Digoxin for cardiomyopathy, serious and/or refractory.
• Antipsychotic drugs for schizophrenia in the acute phase (psychotic relapse), and benzodiazepines to manage agitation.
• Use of benzodiazepines in cases of drug and alcohol withdrawal.
• Selective serotonin reuptake inhibitors and benzodiazepines for panic disorder.

Potentially Inappropriate Medications

Clinical pharmacists identified the use of at least one PIM in 588 (98.2%) admissions of older people in ICUs according to 2012 Beers Criteria, with the median being three (IQR 2–4) PIM/person, ranging from zero to eleven. Of the total number of medications used (n=10140), 1864 PIMs (18.4%) were detected in the sample during the ICU stay: most of which were independent of diagnosis (n=1554). Prescription of metoclopramide (28.6% of PIMs) accounted for the greater number of PIMs detected, followed by benzodiazepines (8.4%), antipsychotics (8.3%) and amiodarone (7.8%). The list of medications to be used with caution in older adults was also evaluated; 289 prescriptions of this type were found. Warnings are provided most frequently for selective vasodilators (85.1%) and serotonin reuptake inhibitors (9.0%). These data are shown in detail in Table 2.

Of the PIMs, 24.8% (462/1864) were newly started in the ICUs, and the most common types were metoclopramide (131), sliding scale insulin (63), diazepam (42), mineral oil (34) and haloperidol (28). After the individual's clinical circumstances that motivated the prescription of a PIM were considered, 137 (29.6%) PIMs were found to be "appropriate", i.e., demonstrated a clinical justification for their prescription in ICU, as can be seen in Table 3.

A total of 204 (10.9%) PIMs were continued during hospitalization after discharge from the ICU to the wards, and 74 (3.9%) were prescribed upon hospital discharge. Of the PIMs most often prescribed upon hospital discharge, 41.1% were initiated in the ICU, 20.5% were started in the wards before ICU admission and 42.5% were present before hospital admission.

In the bivariate analysis, there was a statistically significant correlation between the number of PIM and the hospital length of stay (p<0.001), ICU length of stay (p<0.001), days of delirium (p<0.003), total number of drugs prescribed (p<0.001) and

number of comorbidities (p<0.001) (Table 4). In the multivariate analysis, the number of prescribed PIMs was significantly associated with ICU length of stay and total number of medications (Table 5). The coefficient of determination (R²) of the model was 0.309.

Beers Criteria and Adverse Drug Reaction

Among the 185 patients that were randomly selected, 49 possible drug-related incidents were identified throughout the hospital stay. There was at least one ADR identified in 17.8% (n=33) of admissions, and 16 ADRs were identified as a cause of hospital admission (8.6%). Five patients with the reported reactions evolved to death, all occurred during ICU stay.

Of the 49 ADRs identified, 23 (46.9%) were attributed to medications listed among the Beers Criteria (Table 6). Non-cyclooxygenase-selective non-steroidal anti-inflammatory drugs (NSAIDs) were the most common types of PIM-ADRs (n=5). Most of the ADR-related hospital admissions (six patients) were attributed to drug-induced upper gastrointestinal bleeding, with four cases assigned to NSAIDs and two cases assigned to aspirin. There was no statistical association between number of PIMs and the occurrence of ADRs.

DISCUSSION

The fastest-growing group treated in the ICU is older adults: a vulnerable population frequently given PIMs.⁸ Although significant attention has been focused on reducing PIMs in community-dwelling elderly adults, this is typically not the case for patients hospitalized or those in the ICU. Our primary finding is the high rate of PIM use identified in 98.2% of critically ill older patients. The prevalence of PIM use in this study conducted in Brazil is one of the highest compared to other countries, which report a prevalence of PIMs ranging from 16–49% in the hospitalized elderly.¹³⁻¹⁵ In two other studies conducted with critically ill elderly patients, PIMs were prescribed to over 80%⁸ and 95%¹⁶ of patients, respectively. The high degree of variability in prevalence outcomes is clear. Among the several factors that might be related to this finding, the critical nature of hospitalized patients in these units can be highlighted. Differences in availability of certain drugs and prescribing habits also may account for the major share of differences.

Our data suggest that most of the participants used multiple medications, which was a factor associated with a higher probability of PIM use. In addition, there was a positive correlation between the

Table 4. Correlation between number of potentially inappropriate medications and other variables in the elderly hospitalized in intensive care units.	
Variable	R
Age	-0.025 (p=0.537)
Hospital length of stay	0.313**
ICU length of stay	0.384**
Days of delirium	0.215*
Total number of drugs	0.284**
Number of comorbidities	0.359**
ADR occurrence	-0.010 (p=0.891)
*p<0.05; **p<0.01; R, correlation coefficient; ICU, intensive care unit	

Table 5. Influence of different variables on the number of potentially inappropriate medications, evaluated through multiple linear regression (Number of PIMs; R²=0.309)

Variable	beta value (95% confidence interval)	standard error	p-value
Age	-0.019 (-0.045 a 0.007)	0.013	0.152
Hospital length of stay	0.002 (-0.005 a 0.009)	0.004	0.648
ICU length of stay	0.082 (0.051 a 0.112)	0.015	< 0.001
Days of delirium	0.103 (-0.007 a 0.213)	0.056	0.067
Total number of drugs	0.167 (0.109 a 0.225)	0.029	< 0.001
Number of comorbidities	0.080 (-0.028 a 0.188)	0.055	0.145

PIM, potentially inappropriate medications; ICU, intensive care unit

number of PIMs and the number of comorbidities. The relationship between multimorbidity and polypharmacy is well described in the literature, and several studies have identified a positive association between the number of drugs and the use of PIM.^{9,15,17,18} The multivariate analysis showed that length of ICU stay had a positive influence on the number of PIMs used by acutely ill older patients. A known complication of critical illness and its treatment that often older adults have is a significant increase in psychological symptoms, sleep cycle alterations, delirium and neurocognitive impairment, which may be associated with increased prescription of specific PIMs, such as antipsychotics or benzodiazepines¹⁹⁻²¹, classes that are among the main PIMs started and used in the ICUs of the current study.

Thereby, an important feature of this study was re-assessing the appropriateness of each PIM prescribed in the ICUs based on the clinical circumstances of each patient. There is considerable physiological heterogeneity in older adults, and medications considered potentially inappropriate for one patient population may be appropriate in another based on an individual's clinical status, previous failure with other treatments or the lack of acceptable alternatives.^{19,22} In this study, PIMs were appropriate in almost 30% of the prescriptions in ICU, given the individual's clinical conditions described in medical records.

However, even though these PIMs may be appropriate during the ICU stay, the indications for their use are usually temporary. Failing to discontinue such medications before hospital discharge could be potentially harmful in the post-hospital discharge period and in the long-term.²³ It was recently found that 85% of elderly ICU survivors were discharged from the hospital on at least one PIM, and 50% of PIMs were prescribed in the ICU stay.^{19,24} In the current study, more than 40% of PIMs prescribed upon hospital discharge

were newly started in the ICU. Thus, care should be taken to identify and discontinue PIMs during major transitions throughout the course of hospitalization and determine which PIMs should be discontinued before hospital discharge and which are appropriately prescribed.

The use of PIMs has been considered a frequent cause of ADRs, which are responsible for many geriatric hospital admissions. Older patients may be at a greater risk for PIM-ADRs during periods of acute illness and reduced physiologic reserve.²⁵ In addition to the negative clinical and humanistic aspects that the use of PIMs might cause, they also increase the demand on financial resources for the health system.²⁶ In this study, the rate of ADRs identified was 17.8% and most drugs that were possibly related to ADRs were also considered inappropriate for the older people (46.9% of the identified ADRs were assigned to PIM). Studies show that ADRs cause approximately 5% of hospital admissions in the general population, but the percentage rises to 10% in the elderly.²⁷ Matanovic and Vlahovic-Palcevski, in a study of 454 older people admitted to a university hospital, found that admission was drug-related in 11% of patients²⁸, which is in concordance with our finding of 8.6%. An important cause of ADR-related hospital admission was upper gastrointestinal tract bleeding associated with the use of NSAIDs. It is known that NSAIDs are commonly used by the elderly for chronic pain syndromes, and this age group is particularly at a high risk for NSAID-related ADRs.²⁸ NSAIDs were also the most common type of PIMs implicated in ADRs during the hospital stay. Another important finding of this study is the occurrence of falls associated with the use of benzodiazepines, a serious problem for older adults and a leading cause of functional decline, hospitalizations and injury-related death.²⁹ Other studies have reported that drugs involved in most of the ADRs in the elderly were cardiovascular drugs,

Table 6. Potentially inappropriate medications (according to 2012 Beers Criteria) associated with an adverse drug reaction (n=23)

PIM	N. of ADRs (% of all ADRs)	Description of ADR
Non-cox-selective NSAIDs	5 (10.2)	Upper gastrointestinal bleeding
Benzodiazepines	4 (8.2)	Falls with fractures; depressed mental status
Digoxin > 0.125 mg/day	4 (8.2)	Cardiac arrhythmias and visual disturbances due to digoxin poisoning
Sliding scale insulin	2 (4.1)	Hypoglycemia
Vasodilators	2 (4.1)	Syncope and hypotension
Antipsychotics	2 (4.1)	Agitation and confusion; sedation
Amiodarone	1 (2.0)	Blue-gray skin pigmentation
Dexchlorpheniramine	1 (2.0)	Drowsiness and confusion
Clonidine	1 (2.0)	Hypotension
Metoclopramide	1 (2.0)	Hyperprolactinemia

ADR, adverse drug reaction; COX, cyclooxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs

psychotropic agents and anti-inflammatory drugs^{15,30}, as was also determined in our study.

Although this study used the most updated Beers Criteria at the time of data collection, a multivariate analysis showed no relation between number of PIMs and ADR occurrence. Possible explanations for the lack of association in our study between PIMs and the risk of adverse clinical outcome, could be the sample size, the status of the patients in ICUs that complicate the assessment of ADRs, the short period of hospitalization in ICUs (impacts on health outcomes could not be observed) and, finally the poor transferability of Beers Criteria outside North America (it includes several medications not available or rarely prescribed in Brazil). Several other studies failed to find any significant association between use of Beers listed PIMs and health outcomes.^{11,13,17,30}

This study has limitations that should be considered. Our study was conducted retrospectively at a single-center, so the results may not be generalizable to other ICU patients. Also, there is an inherently subjective level in the process of classification of ADRs. All of the ADRs in our

study were categorized as described in the patient's medical record. If information for any individual item was unavailable or uncertain, a score of zero was coded.

CONCLUSIONS

This study showed a high prevalence of the use of PIMs in critically ill older patients and that, although many PIMs had a clinical circumstance that led to their prescription during the course of ICU hospitalization, many were still present upon hospital discharge. Despite more than 40% of ADRs being attributed to PIMs, there was no statistical correlation between the number of PIMs and the occurrence of adverse reactions. The findings of the current study serve to reinforce the importance of medication safety as a relevant concern during this period of high vulnerability for older adults.

CONFLICT OF INTEREST

Authors declare that there are no competing interests.

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