INTERNAL MEDICINE JOURNAL

doi:10.1111/imj.13961

Hospitalisation and morbidity due to adverse drug reactions in elderly patients: a single-centre study

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Key words
adverse drug reaction, elderly, hospitalisation, polypharmacy, internal medicine.

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Received 14 November 2017; accepted 28 April 2018.

Abstract

Background: Adverse drug reaction (ADR) is a leading but under-recognised cause of illness, particularly in frail subjects with multiple comorbidities.
Aim: To investigate the frequency, patterns and outcomes of ADR as a cause of hospitalisation in elderly patients admitted to an internal medicine ward.
Methods: We performed a retrospective observational study including every patient aged over 65 years who was admitted to our department during a 12-month period. Patients admitted to short-stay (<24 h) observation unit were excluded.
Results: ADR accounted for 106 of total 1750 recorded admissions, which constituted a proportion of 6.1% (95% confidence interval 5.0–7.3%). The median age of patients was 83.5 (78.0–87.0) years and 56.6% were on polypharmacy. A total of 170 ADR was recorded with 45.3% of subjects experiencing concomitantly more than one ADR from a single molecule. Diuretics were the most commonly imputed molecules (30 events, 17.6%), followed by antithrombotics (25 events, 14.7%) and central nervous system-active drugs (16 events, 9.4%). Interactions were judged responsible for 39 cases of ADR (36.8%). An unfavourable outcome was observed in about one-third of patients (37.7%). Among those subjects, 11 (10.4%) died and 29 (27.4%) had residual disability.
Conclusion: ADR are a common cause of hospital admission in elderly patients and are often associated with adverse outcomes. Our data underline the need of appropriate strategies aimed at identifying high-risk patients and avoiding potentially preventable drug toxicities.

Funding: None.
Conflict of interest: None.

Introduction

Adverse drug reactions (ADR) are common but under-recognised causes of hospitalisation and morbidity.[1] Risk factors for ADR include cognitive impairment, chronic kidney disease (CKD), poor nutritional status and complex polypharmacy with high risk of drug–drug interactions.[2] These factors usually co-exist in frail elderly patients typically admitted to the internal medicine departments and a high suspicion index is needed for appropriate diagnosis and treatment. Despite renewed focus on appropriate drug prescription from guidelines and local recommendations,[3,4] patients with unnecessary and potential harmful chronic treatments are often observed in clinical practice.[5,6] This suggests that awareness about the burden of ADR in frail subjects is still limited. The aim of the present study was to investigate the frequency, patterns, severity and outcomes of ADR as a cause of hospitalisation in patients admitted to our department, an internal medicine ward of a secondary care hospital where a large proportion of elderly patients with multiple comorbidities is generally observed. In this setting, better strategies for recognition and prevention of ADR are needed.

Methods

Study design and population

We performed a retrospective observational study in which we included every patient aged over 65 years who was admitted to our department (Internal Medicine Unit, 'C. Magati' Hospital, Scandiano, AUSL Reggio Emilia, Italy) over a 12-month period (from 1 July 2015 to 20 June 2016). The reasons for admission, clinical courses and final diagnoses were reviewed to determine if the admission had been caused by an ADR. Patients admitted to short-stay (<24 h) observation unit and/or with incomplete medical records were excluded. Medication history was obtained from electronic medical records. The number of medications was calculated by the addition of each medication as one unit, with fixed combinations calculated as two medications if available also as single-molecule products. Cardiovascular disease was defined as history of coronary artery disease, peripheral artery disease, transient ischaemic attack or stroke. Arterial hypertension was considered if there was a positive history and/or ongoing antihypertensive treatment. CKD was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 using the CKD Epidemiology Collaboration (CKD-EPI) formula. Anaemia was defined as a haemoglobin concentration below 120 g/L in women and below 130 g/L in men. Chronic liver disease was defined as liver cirrhosis or chronic viral hepatitis. Cancer patients included those with haematological or solid neoplasms (except non-invasive skin cancer) diagnosed less than 5 years before or those with active disease. The presence of other clinically relevant comorbidities, including neurodegenerative disease, diabetes mellitus, psychiatric disorders, autoimmune disease and chronic obstructive pulmonary disease was also recorded from data in electronic medical records. The study protocol was approved by the local ethics committee and performed in accordance with the principles embodied in the Declaration of Helsinki.

Definition and assessment of ADR-related hospitalisation

We considered an ADR as 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function', according to the World Health Organization definition.[7] The Naranjo algorithm was used to assess the causality of the relation between drug use and hospitalisation.[8] ADR observed during the hospital stay or those due to deliberate overdose were excluded. An ADR was defined as 'causal' if it was judged directly responsible for the admission or 'coincidental' if it was a contributory cause in association with competing factors. A drug–drug interaction was considered if it was listed either in the summary of product characteristics or in relevant literature. The assessment of ADR severity was based on the scale of Karch and Lasagna, which classifies events into minor, moderate, severe and lethal.[9] The outcomes were classified as favourable (complete recovery) or unfavourable (death or disability). Disability was defined as an acquired temporary or permanent impairment of physical or mental function.

Statistical analysis

Data are expressed as median (interquartile range) for continuous variables and frequencies (proportions) for categorical variables, unless otherwise specified. The ratio between ADR-related admissions and total admissions during the study period was calculated and the 95% confidence intervals (CI) were computed using the Wilson method. Comparisons between groups were made with the Fisher exact test or Pearson Chi-squared test for categorical variable. Only two-tailed probabilities were used for testing statistical significance. *P* values lower than 0.05 were regarded as statistically significant. All calculations were made

using SPSS Statistics v. 21 (IBM, Armonk, NY, USA) and R-project (R Foundation for Statistical Computing, Vienna, Austria).

Results

ADR-related hospitalisations: prevalence and patients' characteristics

A total of 1750 admissions was recorded at our department during the 12-month study period. Among these, 106 were identified as ADR-related in elderly patients, constituting a proportion of 6.1% (95% CI 5.0–7.3%). The demographic and clinical characteristics of these patients are summarised in Table 1. Patients had advanced age and there was a slight prevalence of women. All subjects had at least two comorbidities, with a consistent proportion of patients with dementia and/or CKD. More than half of patients were on polypharmacy, defined as taking more than six drugs (60 subjects, 56.6%), and 19 subjects (17.9%) were taking more than 10 medications. Ongoing drugs at time of hospital admission are listed in categories and relative frequencies in Table 2. Patients admitted with an ADR had a median stay of 4 days (interquartile range 3–6 days).

Adverse events and causative drugs

Among the identified patients, a total of 170 ADR was recorded. Forty-nine subjects (45.3%) experienced concomitantly more than one ADR from a single molecule. Based on the Naranjo score, the ADR were probable in 28 cases (16.5%), possible in 69 cases (65.1%) and definite in nine cases (8.5%). In 81 cases (76.4%), the ADR was judged 'causal' in respect of hospitalisation, whereas it was considered 'coincidental' in the remaining cases (25 subjects, 23.6%). The frequency of ADR according to the causative drugs is reported in Table 3. Electrolyte disorders and/or volume depletion triggered by diuretics was the most prevalent ADR (43 events, 25.3% of total ADR). Diuretics were the most commonly imputed molecules (30 events, 17.6%), followed by antithrombotics (25 events, 14.7%) and central nervous system (CNS)-active drugs (16 events, 9.4%). About two-thirds of bleeding events were caused by vitamin K antagonists (VKA; 16 events, 9.4% of total ADR). Diuretics and antihypertensives were the most common causes of acute kidney injury (17 events, 10% of total ADR) and syncope (13 events, 7.6%). CNS-active drugs were most frequently imputed in altered state of consciousness (16 events, 9.4%) and electrolyte disorders (five events, 2.9%). Antibiotic-related ADR included gastrointestinal toxicity (two events, 1.2%) and altered state of consciousness (one event, 0.6%).

Table 1 Demographic and clinical characteristic of patients admitted for adverse drug reaction

Variables	Patients (n = 106)
Age (years)	83.5 (78.0–87.0)
Male gender, *n* (%)	47 (44.3)
Number of medications	6 (5–8)
Comorbidities, *n* (%)	
Arterial hypertension	69 (65.1)
Cardiovascular diseases	64 (60.4)
Anaemia	59 (55.7)
Dementia	53 (50.0)
Chronic kidney disease	37 (34.9)
Depression	29 (27.4)
Diabetes mellitus	29 (27.4)
Cancer	25 (23.6)
Autoimmune disorders	19 (17.9)
COPD	15 (14.2)
Chronic liver disease	5 (4.7)
Number of comorbidities	4 (3–5)

COPD, chronic obstructive pulmonary disease.

Table 2 Ongoing therapies at time of hospital admission

Drugs	*n* (%)
Antihypertensives	69 (65.1)
Antithrombotics	64 (60.4)
CNS active drugs	60 (56.6)
Diuretics	55 (51.9)
Beta-blockers/anti-arrhythmics	53 (50.0)
Antidiabetics	25 (23.6)
Proton pump inhibitors	23 (21.7)
Statins	16 (15.1)
Hormonal therapies	12 (11.3)
Analgesics	11 (10.4)
Immunosuppressors	9 (8.5)
Dietary supplements/others	17 (16.0)

CNS, central nervous system.

Drug–drug interactions

Interactions were judged responsible for 39 cases of ADRs (36.8%). Most interactions were pharmacodynamic in nature (37 cases, 94.9%). Examples included concomitant use of loop diuretics and either thiazides or renin angiotensin aldosterone system inhibitors causing dehydration (12 cases, 7.1% of total ADR) and acute kidney injury (seven cases, 4.1%), antithrombotics and non-steroidal anti-inflammatory drugs causing bleeding (seven cases, 4.1%) and concomitant use of two or more antihypertensives causing syncope (six cases, 3.5%).

Severity, outcomes and clinical decisions

An unfavourable outcome was observed in about one-third of patients (37.7%). Among those subjects,

Table 3 Frequency of adverse drug reactions according to the causative drugs

Adverse drug reactions	*n* = 170
Electrolyte disorders	28 (16.5)
Diuretics	18 (10.6)
Psychoactive drugs	5 (2.9)
Dietary supplements	2 (1.2)
Others	3 (1.8)
Dehydration	27 (15.9)
Diuretics	25 (14.7)
Others	2 (1.2)
Bleeding	25 (14.7)
Vitamin K antagonists	16 (9.4)
Antiplatelets	6 (3.5)
Direct oral anticoagulants	2 (1.2)
Non-steroidal anti-inflammatory drugs	1 (0.6)
Altered state of consciousness	22 (12.9)
Benzodiazepines	7 (4.1)
Antidepressants	6 (3.5)
Other psychoactive drugs	3 (1.8)
Antibiotics	2 (1.2)
Others	3 (1.8)
Acute kidney injury	20 (11.8)
Diuretics	16 (9.4)
ACE-I	1 (0.6)
Others	3 (1.8)
Syncope	15 (8.8)
Antihypertensives	7 (4.1)
Diuretics	6 (3.5)
Others	2 (1.2)
Elevated INR	6 (3.5)
Vitamin K antagonists	6 (3.5)
Gastrointestinal toxicity	6 (3.5)
Antibiotics	2 (1.2)
Dietary supplements	3 (1.8)
Opioids	1 (0.6)
Falls	5 (2.9)
Antihypertensives	3 (1.8)
Diuretics	1 (0.6)
Psychoactive drugs	1 (0.6)
ECG abnormalities and/or arrhythmias	5 (2.9)
Beta-blockers	4 (2.4)
Cilostazol	1 (0.6)
Hypo-/hyperglycaemia	4 (2.4)
Corticosteroids	2 (1.2)
Oral hypoglycaemic agents	1 (0.6)
Insulin	1 (0.6)
Respiratory disease	4 (2.4)
Immunodepressants	2 (1.2)
Psychoactive drugs	2 (1.2)
Haematological toxicity	3 (1.8)
Targeted therapies	2 (1.2)
Chemotherapy	1 (0.6)

ACE, angiotensin-converting enzyme; ECG, electrocardiography; INR, international normalised ratio.

11 (10.4%) died and 29 (27.4%) had residual disability. The remaining 66 subjects (62.3%) underwent to complete recovery. The rates of unfavourable outcomes according to causative drug class are shown in Figure 1. ADR provoked by antithrombotics, immunosuppressors or diuretics had the worst outcomes. The proportion of patients who completely recovered was higher in those presenting with syncope (100% vs 56%, $P < 0.0001$) or altered state of consciousness (81.8% vs 57.1%, $P = 0.027$), as compared to other presentations. On the contrary, the higher proportion of poor outcomes was found in patients presenting with bleeding (56.0% vs 32.1%, $P = 0.029$). In 90 cases (76.4%), the imputed drug was completely stopped. In the remaining cases, it was resumed at discharge by reducing dose (17 patients, 16.0%) or, less frequently, at the initial dose (four patients, 3.8%). Overall, 13 ADR were classified as mild (12.3%), 53 as moderate (50.0%), 29 as severe (27.4) and 11 as lethal (10.4%).

Discussion

In the present study we found that ADR occurring in elderly patients accounted for a consistent proportion of hospital admissions in an internal medicine ward. Our data are consistent with previous reports from Italy and other European countries in which elderly subjects presenting with an ADR constituted from 3% to 15% of total admissions.[1,10–13]

Older people are at increased risk of drug toxicity.[2,3] Age-related pathophysiological changes in drug disposition and pharmacodynamic responses lead to increased potential for ADR.[14] Ageing is also associated with increasing number of medications, which is proportionally related to the risk of drug–drug interaction, compliance issues and adverse outcomes.[2,6] A high rate of inappropriate prescription has been reported in literature[15] and two-thirds of ADR were judged avoidable.[1] Consistent with these data, more than half of patients in our study were taking six or more drugs despite a high prevalence of established risk factors for drug toxicity such as advanced age, neurodegenerative disorders and CKD. In addition, drug–drug interactions were involved in approximately one-third of the recorded ADR. Taken together, these data underline that a proactive review of ongoing medications is periodically needed in older patients to identify and remove inappropriate prescriptions, potentially harmful drug–drug interactions, and to check adequate compliance.

Attention should be paid to patients taking diuretics, which were the most common cause of ADR both in our study and in the literature.[1,16] Diuretics are one of the most commonly prescribed class of drugs in the elderly, with loop diuretics accounting for up to two-thirds of prescriptions.[17] Loop diuretics remain the cornerstone

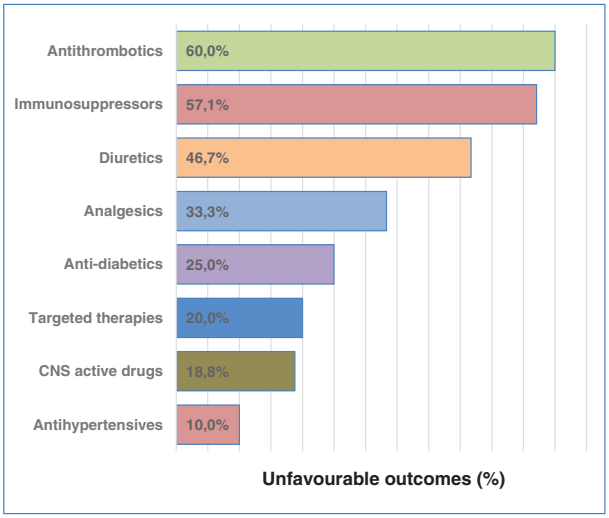

Figure 1 Rates of unfavourable outcomes according to drug class. CNS, central nervous system.

therapy for symptom relief in heart failure, but their use is sometimes extended to patients without a clear indication.[17] Thiazides are also widely used as antihypertensive molecules, despite other classes of antihypertensives revealed at least equally effective and possibly safer, especially in older subjects.[18]

A periodic assessment of risk-to-benefit ratio should also be performed in patients taking antithombotics, especially those treated with VKA.[19] We found in fact that bleeding was the second most common cause of ADR-related admission, with VKA accounting for up to two-thirds of events. In addition, antithrombotic-related ADR are associated with high risk of death and/or disability. Balancing the thromboembolic and haemorrhagic risk is a challenging issue as there is a large overlap between risk factors, especially in elderly patients.[19] Therefore, an accurate risk–benefit assessment that goes beyond the mere risk stratification scoring is needed in frail patients to maximise the safety of this treatment.[20]

CNS-active drugs are also commonly prescribed in older subjects despite a narrower therapeutic index and extremely variable dose–response curve from patient to patient.[21] In our study more than half of patients were taking at least one psychoactive therapy and this class of drugs accounted for about one of every six ADR-related hospitalisations. Most adverse events due to CNS-active drugs that we observed were reversible after drug washout and generally associated with favourable outcome. Nevertheless, caution should be used in prescribing psychoactive drugs in older patients in order to avoid drug–drug interactions, increased risk of falls, delirium or excessive sedation.

Antimicrobials are routinely listed among drug classes deemed to confer a high-risk for ADR.[22] Inappropriate overuse of antibiotics is also the main driver of increasing antimicrobial resistance. A strong adherence to antibiotic stewardship principles is promoted at our department and this may explain the relatively low prevalence of ADR related to the use of antimicrobials in our study. Only few cases of toxicity caused by immunosuppressive drugs or chemotherapy were recorded due to the limited use of these drugs in subjects with advanced age and multiple comorbidities. Similarly, the number of hypoglycaemic episodes that we observed was lower than those reported in literature, probably because we excluded patients admitted to our short-stay observation unit.[23] In fact, at our department, most patients with symptomatic hypoglycaemia are usually discharged within 24–48 h.

As stated before, drug–drug interaction accounted for a consistent proportion of ADR both in literature[1,2] and in the present study. It should be remarked that the interactions most commonly leading to drug toxicity should be well acknowledged among prescribing physicians and included concomitant use of two or more classes of diuretics, antihypertensives or association between antithrombotics and non-steroidal anti-inflammatory drugs. Therefore, if unavoidable, the concomitant use of these molecules should be limited to selected patients with active surveillance and periodic review of benefit–risk ratio.

The in-hospital mortality rate observed in our study was similar to those previously reported in literature.[1,10–13] In addition, one-quarter of patients had permanent or temporary disability at time of discharge. The imputed drug was also completely stopped in the majority of cases, and this could have led to further long-term morbidity and mortality from unprevented events.

Some limitations of the present study should be acknowledged, including its retrospective nature and the limited population number. In addition, some patients with more complex diseases might have been transferred to our referral centre directly from the emergency department, thus restricting the spectrum of observed diseases and/or outcomes. In addition, we did not evaluate the burden caused by ADR occurring while patients are in-hospital or after discharge, or ADR in primary care that were managed as outpatients and did not result in hospital admission.

Conclusion

Our results further reinforce our observation that ADR occurring in elderly patients are a common cause of hospitalisation in internal medicine departments. Therefore,

appropriate strategies aimed at identifying high-risk patients should be developed to avoid potentially preventable drug toxicities, which could be associated with poor outcomes. In particular, clinicians should try to avoid the non-critical perpetuation of unnecessary and potentially harmful treatments in the absence of clear indications or if the benefit–risk ratio is not favourable. Finally, a high suspicion index based on adequate knowledge of local epidemiology is needed for prompt diagnosis and appropriate treatment.

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