The burden and risk factors for adverse drug events in older patients – a prospective cross-sectional study

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Objective. To determine the burden and risk factors for adverse drug events (ADEs) in older patients.

Design. A prospective cross-sectional study.

Methods. Patients (65 years and older) presenting to the tertiary Emergency Unit of Groote Schuur Hospital, Cape Town, between February and May 2005, were assessed for well-established ADEs, as defined by the *South African Medicines Formulary*. Logistic regression models were fitted to determine drugs and other factors associated with the likelihood of developing ADEs.

Results. ADEs were identified in 104 of the 517 (20%) presentations. The most frequently involved drug classes were cardiovascular (34%), anticoagulant (27%), analgesic (19%) and antidiabetic (9%). Patients who developed ADEs were more likely to have five or more prescription drugs ($p < 0.0001$), more than three clinical problems ($p = 0.001$), require admission ($p = 0.04$), and report compliance with medication ($p = 0.02$) than those who did not. Drugs shown to independently confer increased risk of ADEs were angiotensin-converting enzyme inhibitors (RR = 2.6, 95% CI: 1.3 - 5.2, $p = 0.009$), non-steroidal anti-inflammatory drugs (RR = 4.1, 95% CI: 2.1 - 8.0, $p < 0.0001$) and warfarin (RR = 3.1, 95% CI: 1.6 - 6.3, $p = 0.0014$).

Conclusion. ADEs contribute significantly to the burden of elderly care in the Emergency Unit. In a setting such as ours, increased pill burden and certain drug classes are likely to result in increased risk of ADEs in the older population group.

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As humans age, they present to health carers with problems that reflect a combination of specific disease pathologies and individual features of the ageing process. Therapeutic use of prescription drugs is an important intervention in attempts to maintain the health of such individuals. This pharmacological intervention has a price, as an older person (aged 65 years or over) may be at greater risk of suffering iatrogenic adverse effects from the well-intentioned therapy.[1,2]

An injury resulting from the use of a drug is defined as an adverse drug event (ADE).[3] The term 'event' rather than 'reaction' or 'effect' is preferred as it is not always possible to ascribe certain causality to drug-related clinical presentations. Adverse drug events have been identified internationally as a top safety priority since the publication of the influential report by the United States Institute of Medicine in 2000, *To Err is Human*.[4]

As the beneficial effects of drugs are more widely documented, so older patients with a high burden of disease are prescribed increasing numbers of medications, not only for symptomatic relief (e.g. non-steroidal anti-inflammatory drugs (NSAIDs) and digoxin), but also to reduce mortality (e.g. beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and aspirin).[5-8] The use of a greater number of medications increases the risk of an ADE.[1,9] Longitudinal data from Australia show the rate of ADEs to be on the rise, with the age-standardised rate of ADE-related hospital stays increasing from 2.5/1 000 person-years in 1981, to 12.9/1 000 person-years in 2002. The largest increase occurred in those aged 80+, a tenfold increase in men and a sevenfold increase in women.[10]

Ill public sector patients in the Western Cape Province enter the inpatient health system through admission from the EU (EU). Nearly all acute hospital admissions derive from the EU. International data on the presentation of older patients at an EU have identified ADEs to account for between 6.7% and 14.2% of EU visits.[11-15] Up to two-thirds of these ADEs may be preventable.[16] An audit of patients presenting to an EU enables a determination of the impact of clinically significant events that may be causally attributable to a drug. However, little is known about ADEs in the South African EU setting. The present study was therefore conducted to determine the burden of ADEs in older patients presenting for care at an EU, to identify risk factors for these events and to ascertain which drugs pose a higher risk for ADEs.

Methods

A prospective cross-sectional study was conducted of patients aged 65 years and older who presented for treatment and care to the tertiary referral EU of Groote Schuur Hospital (GSH) in

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Cape Town. All medical emergencies presenting to the hospital are assessed and stabilised in the unit. The study included all patients with complete data who presented to the EU between February and May 2005.

Study information was collected using a standard proforma. Data collected included demographic data, detailed drug history including vitamin, herbal and over-the-counter (OTC) medications, a predefined clinical problem list, functional status for basic activities of daily living (BADLs) (independent or having dependence for one or more of the activities of bathing, eating, dressing or transfers), body habitus (as assessed by the primary physician and categorised as either obese, normal, thin or emaciated), medication compliance (self-reported by the patient or caregiver), number of repeat presentations during the study period, and clinical outcome. Acute trauma cases present to a different unit and were not included in the study.

For the purpose of this study an assessment was made by the primary physician and/or the principal investigator (BT) as to whether an ADE contributed to a patient's presentation to the unit. Only well-established ADEs, as defined by the *South African Medicines Formulary* (6th edition), were considered. If an ADE was thought likely, its association was confirmed by causality grading. ADE causality was graded according to published recommendations which grades causation as: (*i*) certain if dechallenge and rechallenge information corroborates causation; (*ii*) probable if only dechallenge information corroborates causation; (*iii*) possible if competing explanations are plausible but less likely than drug causes; and (*iv*) unlikely if the timeline is improbable and an alternative explanation is more likely.[3] ADEs of possible, probable and certain causality were considered as clinically important and analysed.

The study was approved by the Research Ethics Committee of the University of Cape Town's Faculty of Health Sciences.

Statistical analysis

Univariate and multivariate models were fitted to determine factors associated with the likelihood of developing ADEs. The following factors were considered for inclusion in the analysis: age, sex, drug intake, body habitus, functional status for BADLs, number of clinical problems, compliance with medications and number of presentations during the study period. Continuous variables were categorised using their mean value. Factors identified to be significantly ($p < 0.05$) associated with the likelihood of having ADEs in the univariate models were used to build multivariate models. Categorical data were compared using the chi-square test. Statistical analysis was performed using the SAS package, version 8 (SAS Institute Inc., Cary, North Carolina).

Results

Older persons presenting to the EU during the study period comprised 17.5% of all patients assessed in the unit. Of these patients, 18 died before audit data could be obtained. The study included 517 patients. Mean age of the study population was 74 years (range 65 - 95 years). Women comprised 59% of the study individuals.

The average number of clinical problems identified in the study population was 3.2 (range 0 - 6). The average number of prescription drugs used was 4 (range 0 - 10). The average number of OTC/vitamin/herbal preparations taken was 0.5 (range 0 - 5).

ADEs were identified as contributing to 104 of the 517 presentations, a prevalence of 20.1%. Of these 104 ADEs, 42 were of probable causality, while 62 were of possible causality. In 14 presentations, multiple ADEs were identified as having a causal relationship to the patient's presentation.

There was no significant difference in the patients who had ADEs, compared to those who did not, for the baseline characteristics of age, sex, body habitus, functional status for BADLs, use of OTC/vitamin/herbal preparations and the number of presentations made by each patient during the study period. Patients having ADEs were more likely to have five or more prescription medications ($p < 0.0001$), more than three clinical problems ($p = 0.001$) and be compliant with medication ($p = 0.02$) (Table I). Patients having ADEs were more likely to be admitted ($p = 0.04$) and accounted for 74 hospital admissions during the study period.

Cardiovascular drugs – beta-blockers (20 events), ACE inhibitors (10 events), digoxin (8 events), diuretics (3 events) and calcium channel blockers (2 events) – accounted for 36% of the total ADEs. Antithrombotic agents – low-dose aspirin (19 events), warfarin (12 events) and low-molecular-weight heparin (1 event) – caused 27% of ADEs. Analgesic drugs comprising NSAIDs (18 events) and opioids (4 events) accounted for 18% of ADEs, while antidiabetic agents comprising oral hypoglycaemics (9 events) and insulin (1 event) accounted for 8%. The remaining ADEs were caused by central nervous system agents (5 events), immunosuppressive agents (5 events), and antibiotics (1 event).

In a multivariate logistic regression model, the clinical problems that were independently associated with increased risk of having ADEs were atrial fibrillation ($p = 0.014$), diabetes ($p = 0.011$), gastro-intestinal (GI) bleeding ($p < 0.0001$), heart failure ($p = 0.003$) and hypertension ($p = 0.05$). The presence of stroke was negatively associated with an ADE ($p = 0.007$) (data not shown).

Multivariate logistic regression analyses revealed that taking five or more drugs was significantly associated with the presence of an ADE (Table II), as well as ACE inhibitor,

Table I. Baseline demographic and clinical characteristics of patients who had adverse drug events (ADEs) (*N* = 104) and those who did not (*N* = 413)

	Patients with ADE *N* (%)	Patients without ADE *N* (%)	*p*-value*
Age group (yrs)			
65 - 74	62 (60)	236 (57)	
75 - 84	35 (34)	143 (35)	
> 85	7 (7)	34 (8)	
Sex			0.07
Male	35 (34)	179 (43)	
Female	69 (66)	234 (57)	
Body habitus			
Obese	27 (26)	119 (30)	
Normal	23 (22)	65 (16)	
Thin	53 (51)	225 (54)	
Emaciated	1 (1)	4 (1)	
Basic activity			
Independent	71 (68)	282 (68.3)	
Dependent	31 (30)	129 (31.2)	
Unknown	2 (2)	2 (0.5)	
OTC use			
Yes	48 (46.1)	156 (37.8)	
No	56 (53.9)	257 (62.2)	
Prescription drug intake			< 0.0001
< 5 drugs	38 (36)	267 (65)	
≥ 5 drugs	66 (64)	146 (35)	
Presence of clinical problems			0.001
> 3 problems	47 (45)	259 (63)	
≤ 3 problems	57 (55)	156 (37)	
Compliance with medication			0.02
Yes	93 (89)	329 (80)	
No	11 (11)	84 (20)	
Number of presentations			
1	99 (95)	326 (89.6)	
2	3 (3)	35 (9.6)	
3	2 (2)	2 (0.5)	
4	0 (0)	1 (0.3)	

*Chi-square test.
OTC = over-the-counter drugs.

Table II. Factors associated with the likelihood of having an ADE

	Univariate analysis		Multivariate analysis	
Factor	RR (95% CI)	*p*-value*	RR (95% CI)	*p*-value
≥ 5 drug intake	3.2 (2.0 - 5.0)	< 0.0001	2.6 (1.6 - 4.1)	< 0.001
> 3 clinical problems	2.0 (1.3 - 3.2)	0.001	1.5 (0.9 - 2.3)	0.11
Non-compliance	0.4 (0.2 - 0.8)	0.02	0.45 (0.2 - 0.1)	0.09

*Wald's statistic.
Univariate and multivariate logistic regression analysis.

warfarin and NSAID use (Table III). The apparent protective effect of non-compliance against an ADE was not significant in the multivariate analysis.

Discussion

The study findings confirm a high incidence of ADEs in the older patient population presenting to the EU. The rate of 20% is among the highest reported in the literature, possibly because the study was actively seeking ADEs in a group of high-risk patients. However, it is well recognised that the protean manifestations and clinical presentation of ADEs in older patients make it possible that some events may still have been overlooked.

Table III. Drugs associated with the likelihood of having an ADE

Drug	Univariate analysis		Multivariate analysis	
	RR (95% CI)	*p*-value*	RR (95% CI)	*p*-value
ACE inhibitor	2.7 (1.8 - 4.2)	< 0.0001	2.6 (1.3 - 5.2)	0.009
Beta-blocker	1.9 (1.2 - 3.0)	0.004	0.67 (0.3 - 1.3)	0.25
NSAIDs	3.4 (1.9 - 6.2)	< 0.0001	4.1 (2.1 - 8.0)	< 0.0001
Anti-diabetic agents	1.6 (1.0 - 2.5)	0.05	1.2 (0.7 - 2.1)	0.53
Corticosteroids, oral	2.2 (1.0 - 4.9)	0.05	2.3 (0.9 - 5.4)	0.07
Diuretics	1.7 (1.1 - 2.7)	0.02	1.0 (0.6 - 1.7)	0.93
Warfarin	3.8 (2.0 - 7.3)	< 0.0001	3.1 (1.6 - 6.3)	0.001

*Wald's statistic.
ACE = angiotensin-converting enzyme; NSAIDs = non-steroidal anti-inflammatory drugs.
Univariate and multivariate logistic regression analysis.

The large variation in the reported rates of ADEs in the EU (6.7 - 14.2%) may be attributable to methodological differences in the different studies on the causality assessment of ADEs. Recently attempts have been made to standardise ADE terminology and determination, and the present study followed these recommendations.[3]

The emergency room setting places a restriction on the level of causality assessment that can be achieved for any suspected ADE. In this study, levels of 'possible' or 'probable' causality were achieved. 'Certain' or 'definite' levels of causality require the presence of the rechallenge criterion to be satisfied. Rechallenge is often precluded in the EU setting for safety and efficiency reasons. The study showed that age is not a specific risk factor for ADEs; rather the number of concurrent prescription medications is the best predictor for an ADE. The number of coexistent diseases is directly related to the number of medications taken.

Drug classes associated with ADEs in this study have been consistently identified in similar EU studies for their risk of ADEs in older patients. In the literature the reported contribution to ADEs per drug class in the older population are analgesics (NSAIDs and opioids) (15 - 36%), cardiovascular drugs (including diuretics, beta-blockers, ACE inhibitors and digoxin) (5 - 41.8%), anticoagulants (7.9 - 13.3%) and hypoglycaemic agents (6.6 - 31%).[2, 10-15,17,18] Interpretation of the contribution of each drug class to the total burden of ADEs requires caution. The use of no drugs results in no ADEs, while overuse of drugs clearly increases the risk. Any drug-related risk should be clearly weighed against drug-related benefit.

Accumulated trial data show that agents such as beta-blockers, ACE inhibitors, aspirin, warfarin and antidiabetic medications have significant beneficial effects on morbidity and mortality.[6,18-21] Despite optimal prescription and monitoring of these beneficial agents, a certain rate of ADEs will be observed. The number of beta-blocker-related ADEs (17%) in this study suggests that this class of drugs proven to be highly beneficial in ischaemic heart disease and cardiac failure may be incorrectly prescribed, despite an appropriate indication.[6] In the public sector of the Western Cape atenolol and propanolol are the only beta-blockers available at primary and secondary level care. There is insufficient evidence that the use of atenolol or propranolol in heart failure confers the benefit reported with carvedilol or metoprolol. The practice of intra-drug class substitution in the older person in settings where original trial validated drugs are not available may increase the risk of ADEs.

Other drugs used extensively in the older patient have not been shown to offer any survival benefit and are used mainly for symptomatic benefit only. These drugs include NSAIDs, digoxin and psychoactive agents like the tricyclic antidepressants. For these drugs the risks frequently outweigh any benefit, particularly when they are used in patients with significant comorbidity. Increasingly safer substitutes are available, for example using paracetamol for chronic pain, and the newer antidepressant agents in place of the tricyclic antidepressants. In the case of digoxin correct dosage prescription for corrected renal function, or substitution with a beta-blocker for heart rate control, may reduce ADEs.

A patient with an ADE is significantly more likely to require admission. ADEs contributed to 23% of older patient admissions to our hospital during the study period; this rate would account for over 250 admissions yearly at the current rate of ADEs. Data from the UK show that drugs contributed to 11% of hospital admissions of older patients. The data were obtained in the early 80s and 90s, and may not be comparable with recent data as a result of changing prescription trends.[22]

Our study is limited to one tertiary institution so the results may not be generalisable to other facilities. Other study weaknesses are that data were not available for some patients who presented to the EU who may have different characteristics or risk profiles.

Despite the use of causality criteria, the diagnosis of the presence or absence of an ADE remains a subjective assessment and some ADEs may have been overlooked by the medical staff. The cross-sectional design of this study is another limitation, as patients in this study were not followed up beyond their acute assessment.

A strength of this study is the prospective nature and manner in which ADEs were detected by the admitting physician and/or investigator while the patient was still present in the EU. This detection enabled the best evaluation at the time, rather than a judgement made at a later time where information on the event may be incomplete or cannot be extracted from clinical records.

An acceptable rate of ADEs for a drug class versus an unacceptable rate has not been determined and warrants further research, particularly in the context of older persons. Whether some ADEs may have been prevented with more careful monitoring also remains to be determined. In our resource-constrained health care system, cost-saving shortcuts could involve a reduction in monitoring; this approach may prove to be more costly in the longer term.

ADEs are a common contributor to illness in the older person. When assessing an older patient, the possibility of an ADE contributing to the patient's symptomatology should always be borne in mind.

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