Adverse drug reactions in older people

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Adverse drug reactions in older people

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Summary
Adverse drug reactions (ADR) pose significant health-related problems for the older person. Many studies from around the world report a significant incidence of ADR in general and in elderly people in particular, resulting in an increase in drug-related morbidity and mortality. Older people appear to be particularly at risk of experiencing an ADR due to a range of factors, which include polypharmacy, altered drug pharmacokinetic profiles and pharmacodynamic responses, drug interactions and cognitive problems that increase the risk in this patient group. Certain drug classes, such as hypoglycaemic agents and cardiovascular active medicines, have been identified as common causes of ADR. Many studies suggest that the majority of ADR are preventable, so that several different approaches have been tried in an attempt to limit this problem, such as the use of computerized systems to communicate routine issues of patient care, interventions made by pharmacists, spontaneous reporting and continuous education of health care professionals. Whilst all have been shown to reduce drug-related events, identifying individuals at high risk of developing ADR at the point of prescribing by using a risk stratification model could improve the identification and prevention of ADR. This article discusses the clinical impact of ADR in older people and the relative merits of the various approaches tested to date before suggesting areas that require further research.

Keywords: adverse drug reactions, older people, adverse drug events, drug prescribing, adverse event.

Introduction
The importance of patient safety was first expressed by the ancient Greek civilization, when Hippocrates stated that an important tenet of medical care was to abstain from doing harm. It later becomes the most important principle of the Hippocratic Oath – ‘Primum non nocere’ (first do no harm). The likely impact of adverse drug reactions (ADR) were brought to the attention of the public as a result of the severe birth defects noticed following the administration of thalidomide to pregnant women in the early 1960s.¹ Since then a number of high profile incidents, involving medicines, have been reported, which has raised the importance of focusing on the safety aspects of medicines used during the prescribing process. Changes to the population demography in the western world, where people live longer and survive diseases that in the past might have resulted in their death, coupled with the development of a range of new medicines and the use of modern technologies to deliver better care, make prescribing a risky business in an ageing population. Studies in England have shown that 21% of inhabitants are over 60 years of age but receive 56% of all prescriptions dispensed.²,³

Terminology and definitions
Both the terminology and definition used for an ADR often vary across the range of studies undertaken exploring this problem. This creates a difficulty when trying to compare the outcomes of such studies. For example, the term ADR is often used interchangeably with adverse drug events (ADE). An ADE is a general term used to describe any injury resulting from medical intervention relating to a drug.⁴ This definition assumes no direct association between drug and event. Nebekar and colleagues categorized ADE using five different classes: adverse drug reactions, medication error, therapeutic failures, adverse drug withdrawal events, and overdoses.⁵ The World Health Organisation (WHO) defined ADR in 1969 as: ‘A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for modification of physiological functions’.⁶ This definition was recently rewritten because it was considered too vague for routine
application and also included all minor reactions as ADR. The new definition introduced by Edwards and Aronson (2001) includes any reaction that occurs due to a medication error. They defined ADR as: ‘An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.’ This definition has been used in recent studies that enabled the direct comparison of study outcomes. ADR are further classified into type A and B reactions. Type A reaction is common, dose related and related to the known pharmacological action of the drug, whereas a Type B reaction is seen as bizarre and unpredictable. Recently, a new approach to classifying ADR based on dose relatedness, timing, and patients’ susceptibility was introduced.

In this review the incidence, burden, and characteristics of ADR occurring in older patients are discussed. In addition, the different approaches that can be used to reduce the occurrence of ADR are also discussed. PubMed and MEDLINE electronic databases were searched to inform the review. Additional studies were identified by reviewing the references cited in these publications.

Scale of the problem

Recently, concern over drug safety has grown rapidly with several meta-analyses, original research papers and numerous review articles published each year, defining the problem and suggesting approaches to limit the adverse effects of medicines. The risk of drug treatment has been clearly highlighted in published studies, although the incidence and burden of ADR varies worldwide. The diverse outcomes noted were contributed to by a variation in the definition, classification of incidence, causality assessment, and methods used to detect ADR.

Key studies focusing on ADR in older patients can be broadly divided into two main categories: ADR studies focusing on the hospital setting and those in the community setting. Studies conducted in secondary care have largely focused on ADR causing hospital admission, although some report the occurrence of ADR during in-patient stay, especially on general medical and geriatric wards as well as patients seen in the emergency department.

ADR as a cause of hospital admission

Over the past decade, the reported prevalence of ADR causing hospital admission has not changed. A study published in 1991, which drew the attention of the public to the impact of adverse events, reported that 3.7% of 30,195 patients admitted to an acute hospital experienced adverse events. Injuries due to medical treatment accounted for 19.4% of adverse events identified in this study.

A seminal paper focusing on adverse drug events (ADE) as a primary outcome reported that the rate of medicine-related risk was 6.5 per 100 adult admissions amongst 4031 medical and surgical inpatients. The mean age for patients included in this study was 51.8 years. Twenty-eight per cent of the events identified were judged as preventable. This prevalence was later confirmed in a systematic review of 68 prospective and retrospective studies, reporting a mean ADR rate of 6.7% (95% CI 6.6–6.8). Another meta-analysis of 68 studies carried out by Dutch researchers demonstrated that the average rate of ADR-related hospital admission was four times higher in studies focusing on older patients (age > 65 years) compared with the non-elderly, 16.6% and 4.1%, respectively. These results were confirmed in a large UK-based study by Pirmohamed and colleagues, where a prevalence of 6.5% (95% CI 6.2–6.9%) in 18,820 admissions was described. Patients admitted with ADR were significantly older (median age 76 years) than those without ADR (66 years), and almost two-thirds (72%) of the ADR identified were considered to be preventable.

In the USA, the overall rate of ADE in the ambulatory care setting focusing on older patients aged 65 years and over was found to be 50.1 per 1000 person-years. Other studies in older patients have shown higher rates, with the incidence ranging from 5.3 to 30.7%. These findings clearly demonstrate that the rate of ADR is higher in older patients when compared with other age groups.

ADR occurring during hospital in-patient stay

An overview of the principle studies examining ADR incidence by location is provided in Table 1. The rate of ADR was reported to be higher in patients during their in-patient stay, although only a small number of studies have been published
<table>
<thead>
<tr>
<th>Study (country)</th>
<th>Setting (study period)</th>
<th>Methodology</th>
<th>Age of patients (number of sample)</th>
<th>Type of admission</th>
<th>Method of assessment of causality</th>
<th>Primary outcome</th>
<th>Incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray et al., 1998&lt;sup&gt;25&lt;/sup&gt; (USA)</td>
<td>St Mary’s Hospital Medical Center, Madison, Wisconsin (15 months)</td>
<td>Prospective patient monitoring and using review of medical chart, and discussion with nursing and medical staff</td>
<td>≥70 years old Mean age = 78.2 ± 6.2 (n = 157)</td>
<td>General medical admissions</td>
<td>One pharmacist assesses causality</td>
<td>ADE in-patients</td>
<td>14.6%</td>
</tr>
<tr>
<td>Hohl et al., 2001&lt;sup&gt;32&lt;/sup&gt; (Canada)</td>
<td>637-bed university adult teaching hospital (12 months)</td>
<td>Retrospective chart review by one physician</td>
<td>≥65 years old Mean age = 78.6 ± 8.4 (n = 283)</td>
<td>Randomly selected 300 patients admitted to emergency department</td>
<td>Two physicians assess causality using algorithm by Karch and Lasagna</td>
<td>ADE in-patients</td>
<td>10.6%</td>
</tr>
<tr>
<td>Azad, 2002&lt;sup&gt;18&lt;/sup&gt; (Canada)</td>
<td>500-bed teaching hospital (3 months)</td>
<td>Prospective medical chart review</td>
<td>&gt;65 years old Mean age = 75.8 (range 65–95) (n = 111)</td>
<td>General medical admission</td>
<td>Three reviewers assess causality using Naranjo algorithm</td>
<td>ADE in-patients</td>
<td>30.6%</td>
</tr>
<tr>
<td>Chan et al., 2001&lt;sup&gt;19&lt;/sup&gt; (Australia)</td>
<td>500-bed public acute care hospital, medical wards (8 weeks)</td>
<td>Prospective medical record review and patient and/or relative interview</td>
<td>≥75 years old Mean age = 81.8 (n = 240)</td>
<td>Acute unplanned admission</td>
<td>Two reviewers using Hallas criteria for causality, severity, and preventability assessment</td>
<td>ADE</td>
<td>DRA = 30.4%</td>
</tr>
<tr>
<td>Courtman et al., 1995&lt;sup&gt;23&lt;/sup&gt; (Canada)</td>
<td>One acute 32-bed medical ward (including 20 geriatric beds) (19 weeks)</td>
<td>Prospective medical chart review by pharmacist</td>
<td>≥65 years old Mean age: not available (n = 150)</td>
<td>All admissions to study ward</td>
<td>Amended Hallas criteria was used for causality</td>
<td>ADE</td>
<td>DRA = 30.7%</td>
</tr>
</tbody>
</table>

DRA, drug-related admission rate.
### Table 1. (continued)

<table>
<thead>
<tr>
<th>Study (country)</th>
<th>Setting (study period)</th>
<th>Methodology</th>
<th>Age of patients (number of sample)</th>
<th>Type of admission</th>
<th>Method of assessment of causality</th>
<th>Primary outcome</th>
<th>Incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham <em>et al.</em>, 1997&lt;sup&gt;21&lt;/sup&gt; (Tayside, UK)</td>
<td>Care of the elderly wards in a number of hospitals (10 months)</td>
<td>Prospective medical and nursing record review by a pharmacist and patient interview</td>
<td>&gt;65 years old Mean age = 78.0 ± 6.9 (&lt;i&gt;n&lt;/i&gt; = 1011)</td>
<td>Admission to care of the elderly wards</td>
<td>Three reviewers assess causality and preventability using Hallas criteria</td>
<td>Drug related problem</td>
<td>DRA = 5.3%</td>
</tr>
<tr>
<td>Lindley <em>et al.</em>, 1992&lt;sup&gt;33&lt;/sup&gt; (Manchester, UK)</td>
<td>Acute geriatric, medical and heart care wards in a 677-bed teaching hospital (10 weeks)</td>
<td>Prospective medical and nursing record review</td>
<td>≥65 years old Median age = 76 years (range 65–98) (&lt;i&gt;n&lt;/i&gt; = 416)</td>
<td>Emergency and scheduled admissions from primary care</td>
<td>Case identification by researcher and verification with other person</td>
<td>ADR</td>
<td>DRA = 6.3%</td>
</tr>
<tr>
<td>Mannesse <em>et al.</em>, 1997&lt;sup&gt;34&lt;/sup&gt; (Netherlands)</td>
<td>5 general medical wards in a 159-bed university hospital (3 months)</td>
<td>Prospective patient interview</td>
<td>≥70 years old Mean age = 78 (range 70–91) (&lt;i&gt;n&lt;/i&gt; = 106)</td>
<td>All admissions excluding patients transferred from other hospitals and readmission within 1 month</td>
<td>Researcher assesses causality using amended Kramer’s algorithm</td>
<td>ADR</td>
<td>DRA = 12%</td>
</tr>
<tr>
<td>Page <em>et al.</em>, 2006&lt;sup&gt;24&lt;/sup&gt; (USA)</td>
<td>University teaching hospital (18 months)</td>
<td>Retrospective medical record review</td>
<td>≥75 years old Mean age = 79 years (&lt;i&gt;n&lt;/i&gt; = 389)</td>
<td>Admission to two internal medicine services</td>
<td>Naranjo algorithm</td>
<td>ADE</td>
<td>31.9%</td>
</tr>
</tbody>
</table>

DRA, drug-related admission rate.
in this area. Studies from the early 1960s reported that 10–20% of patients experienced an ADR during their hospital stay. Smith and colleagues reported, in 1996, that 7% of 20,000 medical in-patients experienced an ADR while in hospital. Other studies have reported varying incidences of ADR; ranging from as low as 0.86% in one Australian study to 37% in a study of older patients in the Netherlands. The large variations reported are likely to be due to the sample size and the location of the individual studies.

A recent study conducted in the UK reported an incidence rate of 14.7% (95% CI 13.6–15.9), when 3695 patient-episodes were monitored for ADR on twelve wards. All patients over 18 years of age were included in the study, and the median age of patients in the ADR group was 72 years (IQR 56–81) compared with 62 years (IQR 41–77) in the non-ADR group. The result of this study suggests that, in the UK, the incidence of ADR has not changed over the last decade.

There are few recent studies investigating ADR that occur during hospital stay in the older patient. Although the incidence of ADE ranges from 10.6 to 31.9%, the majority of these studies focused on patients older than 65 years with sample sizes ranging from 111 to 2814 patients.

Burden of ADR for the patient

Although ADR have been shown to have an impact on patient morbidity and mortality, they also have financial implications. In the USA, ADR is considered among the fourth to sixth cause of death in hospitalized patients, and the seventh most common cause of death according to a recent Swedish survey.

In 2001, a UK government report entitled ‘A Spoonful of Sugar’ denounced the growing incidence of deaths caused by ADR and medication errors, citing a 5-fold increase over a 10-year period. Subsequently, Pirmohamed and colleagues reported that mortality was over 2% in patients admitted due to experiencing an ADR, and when followed for a further 6 months an incidence rate of 0.15% was observed. If these results were applied to the 3.8 million hospitalized patients in the UK, it is estimated that 5700 deaths could be attributable to ADR. Norwegian researchers detected an incidence of fatal ADE of 18.2%, of which 48.1% of all deaths were drug related.

As ADRs are implicated in the morbidity of patients it suggests that there is a worsening of quality of life and that an ADR could contribute to an increase in GP visits, hospital admission and length of hospital stay. A recent study demonstrated that the median length of stay in patients experiencing an ADR was 12 days longer when compared with patients who had not experienced an ADR. Sometimes ADR could be misdiagnosed as a primary medical condition which, in turn, can lead to more medicines being prescribed, further increasing the risk to the patient.

Burden of ADR for the organization

ADR also have financial implications for society and governments. The Audit Commission revealed that ADR and medication errors cost the NHS in England, £0.5 billion annually. Pirmohamed and co-workers estimated that the ADR burden costs £466 million (€706, $847) each year, accounting for 4% of the hospital bed capacity in the UK. In the USA, it has been calculated that ADR-related hospital admissions increase the cost of patient care by $2,262 per-patient. Similarly, the cost of preventable ADR in a 700-bed hospital has been estimated to be $2.8 million per annum. A retrospective USA study, conducted by Rothschild et al., on data retrieved from a New England malpractice insurance company showed that 6.3% of claims made were due to adverse drug events, of which 73% were considered preventable.

Risk of experiencing an ADR

The higher incidence of ADR in older people may be due to several factors, each multidimensional and often interconnected. Polypharmacy (both prescribed and non-prescribed medicines), altered drug pharmacokinetic profiles and/or pharmacodynamic responses as a result of ageing and altered adherence, caused by depression or cognitive impairment, contribute to this increase in risk to older people.

Identifying an ADR in the older patient is often more challenging as the presentation can be both atypical and non-specific as often symptoms of an ADR are ascribed to the onset of a disease or simply due to frailty. For example, falls, delirium, drowsiness, lethargy, light headedness and apathy are frequently attributed as primary diagnoses
Table 2. **Physiological changes in older people**

<table>
<thead>
<tr>
<th>No.</th>
<th>Change in physiological aspect</th>
<th>Causes and changes noticed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reduced hepatic metabolic capacity</td>
<td>(a) decline of liver mass, (b) decreased blood flow, (c) decreased hepatic enzyme activity</td>
</tr>
<tr>
<td>2</td>
<td>Reduction in renal clearance</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Increase in free drug fraction</td>
<td>(a) decreased serum albumin concentration</td>
</tr>
<tr>
<td>4</td>
<td>Change in drug distribution</td>
<td>(a) increased percentage of fat mass, (b) decrease in lean mass</td>
</tr>
</tbody>
</table>

Physiological changes that occur due to ageing may affect drug distribution, metabolism and excretion, even if the drug regimen has not been previously modified. Although these physiological changes are unavoidable in old age they are, to some extent, predictable. Adjustment to drug dosage may be required in older people, which can help avoid Type A reactions. Table 2 summarizes the important physiological changes noticed due to ageing that contribute to the higher risk of ADR. Reduction in hepatic capacity, renal function and changes in body composition may result in pharmacokinetic changes of certain drugs. For example, digoxin dosage may require considerable modification in older people due to the reduction in renal clearance and volume of distribution which then increases the serum concentrations and potential for harm. Changes in the target organ were identified as the main reason contributing to pharmacodynamic alterations in the older person. Alteration in receptor function can result in higher sensitivity at a given drug plasma concentration. The use of benzodiazepines and anti-psychotic agents in older people is associated with higher risk of ADR due to increased sensitivity to these drug classes.

**Altered pharmacokinetic and pharmacodynamic profile**

Physiological changes that occur due to ageing may affect drug distribution, metabolism and excretion, even if the drug regimen has not been previously modified. Although these physiological changes are unavoidable in old age they are, to some extent, predictable. Adjustment to drug dosage may be required in older people, which can help avoid Type A reactions. Table 2 summarizes the important physiological changes noticed due to ageing that contribute to the higher risk of ADR. Reduction in hepatic capacity, renal function and changes in body composition may result in pharmacokinetic changes of certain drugs. For example, digoxin dosage may require considerable modification in older people due to the reduction in renal clearance and volume of distribution which then increases the serum concentrations and potential for harm. Changes in the target organ were identified as the main reason contributing to pharmacodynamic alterations in the older person. Alteration in receptor function can result in higher sensitivity at a given drug plasma concentration. The use of benzodiazepines and anti-psychotic agents in older people is associated with higher risk of ADR due to increased sensitivity to these drug classes.

Drugs in older people are increased by concurrent use of multiple medications, which might contribute to ADR. Davies et al. (2009) found that 59% of the registered ADR were linked to drug interactions, of which 91.7% were classified as pharmacodynamic interactions, 5.3% pharmacokinetic and the remaining 3% with mixed mechanism.

**The prescribing cascade**

Often new symptoms caused by a drug go unrecognized and require the addition of another drug to the patient’s existing therapy. This phenomenon is known as the prescribing cascade. In some cases, the drug treatment can be inappropriate and therefore can increase the risk of further ADR. Difficulties in identifying drug-related symptoms and polypharmacy in older people further increase the likelihood of the prescribing cascade occurring. Examples of common prescribing cascades are shown in Table 3.


**Table 3. Examples of prescribing cascade**

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>Adverse effect</th>
<th>Subsequent treatment</th>
<th>Subsequent adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-steroidal anti-inflammatory</td>
<td>Gastrointestinal upset</td>
<td>Proton pump inhibitors</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Hyperuricaemia</td>
<td>Allopurinol</td>
<td>Hypersensitivity reaction</td>
</tr>
<tr>
<td>Antipsychotic drugs</td>
<td>Extrapyramidal symptoms</td>
<td>Levo-dopa</td>
<td>Nausea, hypotension</td>
</tr>
</tbody>
</table>

**Other contributing factors**

Inappropriate prescribing is reported to be common, especially in older people. Hajjar and colleagues reported that 44% of frail older patients were treated with at least one unnecessary drug and a UK study revealed that almost 50% of ADR could be attributed to inappropriate prescribing.

Certain drug classes such as cardiovascular agents have been shown to increase the risk of ADR 2.4 times compared with other medications. Medication that required therapeutic monitoring (digoxin) was found to be an independent predictor of ADR.

Some conditions commonly observed in older people, such as anaemia, malnutrition, and multipathology, have been recognized to increase the risk of ADR. Due to multiple diseases, prescribers from different specialties can initiate medications used in older patients. According to an expert consensus panel, multiple prescribers represent a potential risk factor for ADE. Other research has further confirmed the number of prescribing physicians as an independent risk factor for patients self-reporting an ADE in the outpatient setting.

A higher risk of developing an ADE has been shown in patients known to have a degree of cognitive impairment (OR 0.94; 95% CI 0.90–0.97). However, a contradictory result was shown in another study where cognitive impairment was associated with a reduced risk of ADR. Difficulties in the identification of ADR in older people and lack of thorough assessment may have contributed to this result. Older people with cognitive impairment also have difficulty communicating their problem to physicians, which further complicates the condition.

**Drug classes causing ADR**

Certain drug classes appear to be recurrently associated with ADR. A systematic review identified six classes of drugs (antibiotics, anticoagulants, cardiac glycosides, diuretics, hypoglycaemic agents, and NSAIDs) as responsible for 60–70% of ADR, causing hospital admission or occurring during hospital stay. A more recent systematic review also highlighted four major drug classes (anti-platelets, diuretics, NSAIDs, and anticoagulants) as causing 50% of preventable drug-related admissions. In the older person, diuretics were identified as the drug class most commonly associated with ADR. These outcomes probably represent the high usage of this drug class in this patient group.

Careful and frequent monitoring should be done when prescribing these high-risk medications in older people. Assessment of the relative risk-benefit for each newly prescribed medication should be carefully considered. For example, the use of drugs with recognized potential to cause harm such as anti-platelets and diuretics should be tailored to individual patient’s needs, as there is growing evidence of their benefits. Dosage and frequency should be tailored based on the changes in physiological functions expected due to the ageing process.

**Preventing ADR**

Implementation of new strategies to reduce the occurrence of ADR seems to be a reasonable and achievable goal. At present, there are two main approaches to preventing ADR: the first is more focused on the analysis of the process of care, while the second is aimed at identifying ‘at risk’ patients.

The first approach focuses on the process of care and presupposes that ADR are closely related to medication errors. Hence trying to minimize the occurrence of errors could help to reduce ADR. This concept has been adopted from Reason’s Swiss Cheese model, which describes a system of failures, highlighting the important role of systems of defence.
In this model, an organization’s defences against failure are modelled as a series of barriers, with individual weaknesses in parts of the system (holes in Swiss cheese), permitting ‘a trajectory of accident opportunity’, so that a hazard passes through all of the holes in all of the defences, leading to a failure. For example, a patient can be administered a drug, despite a history of allergy. This will most likely result in a drug reaction due to re-exposure, which is considered predictable and preventable. There are several preventative measures currently available; for example, use of a computerized system, pharmacy intervention, spontaneous reporting and documentation.

In the second approach, patients’ characteristics are analysed to detect individual risk to tailor subsequent interventions. Due to the complex context, an intervention combining both strategies might be more effective.

**Process of care**

An ADR is classified as preventable if it is due to inappropriate prescribing that includes misuse, overuse or underuse of drugs. Any measures that improve the drug use process can be used effectively to minimize ADR occurrences. Some useful strategies within this aim are the use of an electronic prescribing database, pharmacists’ involvement in patients’ care and spontaneous reporting systems.

**Utilizing computer systems**

The implementation of computerized or information technology (IT) in healthcare systems has been shown to reduce the rates of drug administration errors that indirectly reduces ADR. A computerized system is helpful in obtaining a patient’s record including previous clinical information and also for continuous monitoring of a patient’s condition. Leape and colleagues (1995) identified that lack of patient information at the point of prescribing accounted for 18% of the reported errors. A computerized Physician Order Entry (CPOE) with a Clinical Decision Support System (CDSS) was found to be beneficial, despite several limitations. In CPOE, the medication order is performed online, whereas CDSS is a system that provides advice during the prescribing process. CDSS provides information automatically about drug allergies, interactions, doses and routes. A recent review of five studies highlighted the potential of these systems to reduce medication error.

Implementation of the CPOE system in the actual clinical setting produced a significant decline in the preventable and non-detected ADE: from 10.7 events for 1000 patient days to 4.68 events with a decrease of 84% in transcription errors. Other studies have found an improvement in detecting ADE through computer-based monitoring systems. Nevertheless, there is still a lack of evidence available to confirm that these interventions can be effective in reducing ADR.

**Pharmacy interventions**

Pharmacist knowledge of pharmacology of medicines, particularly of their side-effect profiles, can be useful in preventing ADR. A study conducted on a general medicine unit showed that pharmacist participation in the ward-round team reduced the rate of preventable ADE from 26.5 to 5.7 per 1000 hospital days. Interestingly, 98% of the recommendations by the pharmacist, mainly dose-related changes and adding a new drug to existing therapy, were accepted by the team. A meta-analysis of 32 studies performed on older patients showed that pharmacists’ interventions can increase the understanding and adherence among patients. However, the evidence of benefit in reducing hospital admission and mortality has not been demonstrated, which reflects the suboptimal design of many of the studies undertaken to date.

On the other hand, a significant decrease in morbidity and cost of care were recorded in a randomized controlled study focusing on pharmacist-led medication review of patients over 80 years old. This study was conducted in Sweden. Four hundred patients were randomized into control (n = 201) and intervention (n = 199) groups. The control group received standard care without direct involvement from the pharmacist on the ward, whereas ward-based pharmacists were involved in performing the interventions in the other group. There was an 80% reduction in drug-related readmission, 47% in visits to emergency departments and 16% in all hospital visits. A more
practical solution might be to narrow pharmacists’ assistance to a group of patients recognized as at high risk.

Spontaneous reporting and documentation
Identification and reporting of ADR is key in the prevention strategy. National pharmacovigilance systems such as the Yellow Card System in the UK represent the most important approach for monitoring and detecting ADR-associated factors in medications and patients. It was developed in 1964 and currently includes electronic reporting, and direct reporting by the public. Under-reporting was identified as the main limitation of the system, although a gradual increasing trend has been registered in recent years. Since the introduction of this system, several drugs have been withdrawn, resulting in a reduction of ADR due to specific drugs.

Poor documentation of patients with a history of ADR can lead to re-exposure of the offending drug, causing the patient to re-experience the ADR. Previous occurrence of ADR is an important risk factor for developing ADR. Thus simple intervention, such as emphasizing the importance of accurate documentation of ADR at the time of reaction, and providing relevant information to the patient about ADR, can help to prevent recurrence.

Communication and other interventions
Improving communication between the healthcare provider and patients has been recognized to moderately reduce ADE. A significant reduction in serious ADE was observed in frail and older patients randomized to receive a comprehensive geriatric assessment, compared with the usual care. Providing information and communicating the benefits and risk of medication to patients can improve adherence through shared decision-making based on pharmaceutical need.

Continuous education for healthcare professionals can also help in preventing ADR. Prescribers with up-to-date information on new and high-risk medications, including information on comparative benefits, risk and contraindications, can make the best decision at the point of prescribing.

The introduction of newer generation drugs with a lighter burden of side-effects may reduce ADR. For example, COX-2 inhibitors have a similar anti-inflammatory effect to aspirin and ibuprofen, but a lower gastro-intestinal impact. However, these drugs have since been proven to have adverse cardiovascular effects, necessitating withdrawal of many of this class. Perhaps the best way to prevent ADR is to minimize pharmacological treatment.

There is a growing interest in non-pharmacological treatment, which could be an option to avert ADR. For example, cognitive behaviour therapy and relaxation techniques have been shown to reduce anxiety and therefore anxiolytic usage. Regardless of various methods described that target the process of care, a multifaceted approach involving more than one intervention, which considers the variation observed in individual patients, could be the most effective way to prevent ADR.

Highlighting patients at risk
Identification of subjects at risk of ADR using risk factors such as genetic predisposition or other clinical characteristics is the main approach in this method. Recent advances in pharmacogenetics, especially identification of mutations and polymorphism in genes coding drug-metabolizing enzymes, drug transporters and receptors, has provided an explanation of increased individual susceptibility for ADR.

Ross and colleagues have demonstrated that subjects with genetic variants in the Thiopurine Methyltransferase (TPMT) gene are more prone to severe myelosuppression after administration of azathioprine. It can be fatal in individuals with homozygosis in low activity variants (e.g. TPMT*3A), which reduce inactivation of azathioprine, and lead to accumulation of thioguanine nucleotides in haematopoietic tissues. Variations in the human genome represent an interesting field for further research, but application in routine clinical practice could be limited by high costs and lack of laboratory facilities.

Predicting ADR
A risk stratification approach to preventing an event has been used successfully in different areas. Information about patients, diseases or treatment is drawn prospectively with the aim of stratifying subjects for their risk of developing an
event. The theoretical structure of a predicting model is based on the identification of risk factors and estimation of individual rates of risk and benefit. To date, numerous models have been proposed to predict adverse events. Variation in the outcome measures, methodologies, and level of complexity limits direct comparison between the studies.

Elnicki and Schmitt initiated the hypothesis that each adverse event could be caused by a multiplicity of concurrent factors, but a single risk factor is not enough to predict the occurrence of any adverse event. Another attempt to build a risk model for ADE led to identification of seven variables, whilst previously only two factors had been recognized as significant to predict ADE. However, these models were not used in clinical practice due to low sensitivity and not being validated in different populations.

Recently, Onder and colleagues developed and validated a new predicting tool consisting of six variables to stratify older patients who are at risk of ADR during in-patient stay. Although it was based on secondary analysis using a dataset collected by The Gruppo Italiano di Farmacoepidemiologia nell’Anziano (GIFA), the tool was validated in four different European countries. This increases the generalizability of the model developed.

Conclusion
ADR are relatively common in older patients, and the majority are preventable. In consideration of the recognized impact of ADR on patients’ outcome, quality of life, length of hospital stay, mortality, morbidity and risk of hospital admission, several approaches with the aim of reducing the high incidence of ADR have been proposed.

Accurate identification of ADR, especially detection of preventable ADR, is key to successful prevention strategies. There are multiple methods currently available with the aim of reducing the occurrence of ADR, including trying to identify at-risk patients in order to target additional attention and intervention. Several models are available, unfortunately not validated in bigger, and the UK, populations. The ideal model to predict ADR should include a variety of patients, therapeutic and environmental characteristics. Information and research into genetic susceptibility to ADR would sharpen the predictive ability of the model developed. Any newly developed risk stratification tool should be evaluated using an intervention or well-defined outcome-oriented study. It should be extended by a double blind, randomized trial. Intervention plans should be designed for those patients who are classified as having a higher risk of ADR. Patients should be followed up for the evaluation of several outcome measures including clinical outcomes, length of hospital stay, frequency of ADR, hospital admission, emergency department attendance, changes in quality of life, independence, cognition, and subjective health. To further strengthen the findings, a pharmacoeconomic evaluation of the benefits of the intervention should also be performed.

Future studies should consider the challenges and difficulties that may arise due to the complexity of drugs used in older patients. Inappropriate prescribing, lack of monitoring or drug-taking behaviour are several contributors to medicine-related problems. Clearly, the role of prescriber, pharmacist and patient are inter-related and crucial to the successful implementation of any prevention strategy. Perhaps future study should cover both primary and secondary care, including nursing home and residential homes.

Additional research in this area is a priority to reduce impact of ADR upon patient care, financial cost and reduction of hospital admission and length of stay. Methodological limitations and lack of standardized definition of the primary outcome have proved to be obstacles, and need to be improved in future studies. Clearly, an eclectic multidimensional approach is needed to prevent the occurrence of ADR in older people.

Conflicts of interest
All the authors declare no conflicts of interest.

References


31 van Kraaij DJ, Haagsma CJ, Go IH, Gribnau FW. Drug use and adverse drug reactions in 105 elderly...


45 Mannesse CK, Van Der Cammen TJ. [Adverse drug reactions in three older patients, even without changes in medication]. *Nederlands tijdschrift voor geneeskunde* 2003; 147: 585–87.


Pham CB, Dickman RL. Minimizing adverse drug events in older patients. Am Fam Physician 2007; 76: 1837–44.


