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Adverse Drug Events as a Cause of Hospitalization in Older Adults

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Abstract

Older adults are about four to seven times more likely than younger persons to experience adverse drug events (ADEs) that cause hospitalization, especially if they are women and take multiple medications. The prevalence of drug-related hospitalizations has been reported to be as high as 31%, with large heterogeneity between different studies, depending on study setting (all hospital admissions or only acute hospital admissions), study population (entire hospital, specific wards, selected population and/or age groups), type of drug-related problem measured (adverse drug reaction or ADE), method of data collection (chart review, spontaneous reporting or database research) and method and definition used to detect ADEs. The higher risk of drug-related hospitalizations in older adults is mainly caused by age-related pharmacokinetic and pharmacodynamic changes, a higher number of chronic conditions and polypharmacy, which is often associated with the use of potentially inappropriate drugs. Other factors that have been involved are errors related to prescription or administration of drugs, medication non-adherence and inadequate monitoring of pharmacological therapies. A few commonly used drugs are responsible for the majority of emergency hospitalizations in older subjects, i.e. warfarin, oral antiplatelet agents, insulin and oral hypoglycaemic agents, central nervous system agents.

The aims of the present review are to summarize recent evidence concerning drug-related hospitalization in older adults, to assess the contribution of specific medications, and to identify potential interventions able to reduce the occurrence of these drug-related events, as they are, at least partly, potentially preventable.

1. Introduction

Adverse drug events (ADEs) are the most common type of iatrogenic injuries and a top safety priority. An ADE is defined as 'an injury resulting from the use of a drug'[1] and also includes adverse drug reactions (ADRs), defined as 'a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of

disease or for the modification of physiologic function',[2] as well as harm caused by medication errors (in prescription, administration or monitoring of drug therapy) or patient non-adherence (adherence defined as 'the extent to which patients take the medications as prescribed by their health care providers').[3]

ADEs are a public health problem in older patients. For many years, research focused mainly on ADRs, as they account for the majority of ADE-related hospitalizations.[4] Despite being underreported,[5] ADRs are known to be responsible for 5–10% of hospital admissions,[6,7] although a very recent meta-analysis reported that 2% of adult outpatients being hospitalized or visiting emergency care are the result of an ADR.[8] Indeed, a large heterogeneity has been observed among studies, depending on study setting (only acute or all hospital admissions), study population (entire hospital, specific wards, selected population and/or age groups), type of drug-related problem measured (ADRs or ADEs), method of data collection (chart review, spontaneous reporting or database research), method used to detect ADEs or ADRs.[9]

In particular, studies that consider patients of all ages[10-14] show much lower percentages than those analyzing older age subgroups:[4,6,9,15-20] in older people the odds of being hospitalized for ADR/ADE-related problems is four to seven times higher than in younger people,[9,10,12,21,22] and ADEs have been involved in up to 31% of hospital admissions.[23] Moreover, the number increases with aging[24] and in the past 30 years.[25]

The economic burden of drug-related hospitalizations is also increasing: costs associated with drug-related problems have more than doubled between 1995 and 2000 in the USA and hospital admissions accounted for nearly 70% (US$121.5 billion) of total costs.[26] More recently, the annual costs for ADR-related hospitalizations in Spain have increased from €226 million in 2001 to €272 million in 2006.[10]

As new studies on this topic have recently been published, the aims of the present review are to define the current knowledge on the epidemiology of medication-related hospital admissions in older people as well as to evaluate critically interventions that could be implemented to reduce the incidence of such a phenomenon, which has a negative impact on the health status of older patients and increases healthcare expenditure.[27]

2. Methods

The studies included in this review were collected by means of a systematic PubMed search from 1966 to September 2012, using the following keywords with different combinations: drug-related admission (or hospitalization or problems); medication-related admission (or hospitalization or problems); adverse drug events (or reactions) AND admission (or hospitalization); elderly (or aged [MeSH term]). Limits in this search were English language and the search terms 'drug abuse', 'alcohol abuse' and 'children' (or 'paediatric'). Moreover, the reference lists of retrieved articles were screened for additional pertinent studies. Two authors (F.S. and A.M.) independently reviewed the literature to identify eligible studies and assessed their suitability for inclusion, resolving disagreements by discussion with a third author (A.C.). Studies were further selected if they provided data that estimated the prevalence of medication-related hospitalizations of outpatients. Studies were excluded if they addressed ADEs in patients with a particular disease (e.g. heart failure patients or patients with depression) or during admission, or emergency visits without data on hospitalization.

3. Drugs most Commonly Involved in Adverse Drug Event-related Hospitalizations

3.1 Haematological Agents

This group includes antiplatelet agents and anticoagulant drugs, which are likely to be the drugs most commonly involved in ADE-related hospitalizations (ranging from 5.7 to 42.3%).[11,12,16,19,28-31] The classic clinical presentation is haemorrhage, in particular gastrointestinal haemorrhage, which leads to hospitalization in 85% of cases; warfarin is responsible for more than 75% of all haematological agent-related admissions.[19]

Patients receiving warfarin have a higher risk of all types of haemorrhage compared with patients receiving antiplatelet drugs.[32] However,

it is still controversial whether warfarin increases the risk of haemorrhage compared with dual antiplatelet therapy (DAT), e.g. acetylsalicylic acid plus clopidogrel:[32,33] indeed, the rate of intracranial haemorrhage has been found to be similar between DAT and warfarin, as well as the rate of hospitalization for acute haemorrhage.[32,33] Medical conditions such as heart failure, ischaemic heart disease, chronic kidney disease and stroke increase patient vulnerability to anticoagulant-associated ADEs. As warfarin provides a much higher reduction of thrombotic events compared to antiplatelet agents but older patients have, at the same time, a much higher general risk of bleeding, the prescription of this therapy should be based on an accurate evaluation of the benefit–risk ratio.[34] New anticoagulant agents (dabigatran, rivaroxaban, apixaban) have recently been tested in randomized clinical trials[35-37] and were found to be more efficacious than warfarin for the prevention of stroke and systemic embolism in patients with atrial fibrillation;[38] moreover, apixaban demonstrated higher efficacy than aspirin with a similar safety profile in patients with atrial fibrillation not suitable candidates for warfarin.[39] With a decreased risk of intracranial bleeding, they appear to have a favourable safety profile, making them promising alternatives to warfarin;[38] however, further data are needed, ideally coming from clinical trials specifically performed in older patients, to extend such a consideration to this age group.

Compared to anticoagulant-related bleeding, heparin and low molecular weight heparin-induced thrombocytopaenia is less frequently responsible for hospital admission.[11] Fondaparinux and other factor Xa inhibitors as well as direct thrombin inhibitors have been associated with a much lower likelihood of thrombocytopaenia and can be used in heparin-induced thrombocytopaenia.[40] All these drugs can cause severe bleeding complications in patients with renal failure, therefore their doses must be accurately adjusted in the presence of renal impairment.

Antiplatelet agents cause up to 19.2% of ADE-related hospitalizations,[12,19,28] mainly caused by haemorrhage of the gastrointestinal tract. Aspirin has a higher risk than ticlopidine or clopidogrel alone,[12,41] but among patients with a history of gastrointestinal bleeding, 22% developed bleeding while taking clopidogrel[42] and a meta-analysis reported a rate of gastrointestinal bleeding while taking thienopyridines of 1.6%.[43] Ticlopidine is known to have a higher risk of severe, and even fatal neutropenia, usually being considered second choice;[44] however, prasugrel is associated with a higher risk of bleeding than other antiplatelet agents, especially in older patients.[45] Ticagrelor, a new direct platelet $P2Y_{12}$ antagonist with reversible pharmacological effects on platelet function, was found to be more effective than clopidogrel in elderly patients with acute coronary syndromes and no evidence of an increased risk of major bleeding was noted across multiple groups of patients stratified by age.[46] DAT is associated with a higher risk of bleeding and severe gastrointestinal bleeding, with no increase in fatal events or intracranial haemorrhages.[33,47] Finally, triple therapy (aspirin, clopidogrel and warfarin), used when DAT is required for coronary stenting and anticoagulation is required for atrial fibrillation or mechanical heart valves, was shown to be associated with up to a fivefold higher risk of bleeding in different studies,[48-50] whereas a recent meta-analysis found only a twofold increased risk.[51] Conversely, a significant reduction in ischaemic stroke has been found[51] without an increased rate of bleeding, also in octogenarian patients.[52] In summary, the bleeding risk caused by antiplatelet agents has been hypothesized to be increased in older adults, mainly as a consequence of comorbidity and polypharmacy,[53] but data coming from the few randomized clinical trials that enrolled a sufficiently large number of older patients do not allow a firm conclusion on this point to be drawn.[46,47,51,54]

3.2 Endocrine Agents

This group includes antidiabetic drugs (insulin and oral hypoglycaemic agents) and systemic corticosteroids. It has been shown that they are responsible for 6.6–28% of ADE-related hospital admissions,[11,19,28,29,55,56] with the highest figures in older patients.[19,55]

Nearly all hospitalizations (>90%) attributed to antidiabetic drugs are caused by hypogly-

caemia,[19] defined as blood glucose levels less than 2.8 mmol/L (50 mg/dL) with symptoms or less than 2.2 mmol/L (40 mg/dL) without symptoms. Older patients present more often with neuroglycopaenic symptoms (dizziness, weakness, confusion, nightmares, delirium) than adrenergic symptoms (sweating, palpitations, tremors). Indeed, hypoglycaemia associated with altered mental status or other neurological sequelae or with loss of consciousness or seizure are the main presentations in older adults.[19] Falls and fractures, as well as cardiovascular consequences (myocardial ischaemia, malignant ventricular arrhythmias or other proarrhythmic effects) are also possible. Polypharmacy (e.g. beta-blockers can suppress the symptoms of hypoglycaemia); drug interactions (e.g. oral hypoglycaemic agents with insulin or with gatifloxacin or trimethoprim/sulfamethoxazole);[19,57,58] renal failure (by reducing clearance of oral agents); visual and, particularly, cognitive impairment (by reducing diabetes self-management ability) are significant determinants in the increased risk of developing hypoglycaemia of older patients.[59] In some patients, cognitive decline has also been considered to be a consequence of repeated episodes of hypoglycaemia.[60]

Insulin causes hypoglycaemia that requires hospitalization more often than oral hypoglycaemic agents.[11,19] The analogue formulations offer several advantages over human insulins, including more convenient dosing, faster onset, more consistent duration of action and a possible reduction in the risk of hypoglycaemia.[61] Among hypoglycaemic agents, long-acting sulfonylureas (chlorpropamide, glimepiride, glyburide) have the greatest risk of causing hypoglycaemia[62] and should be avoided in older patients, especially when considering that several valid alternatives are available.[63] Metformin (which has not been associated with hypoglycaemia) or, if not tolerated or contraindicated, short-acting sulfonylureas (glipizide or repaglinide if there is chronic kidney disease) should be the first choice for oral treatment of type 2 diabetes in these patients. Glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors (i.e. incretins), by stimulating insulin secretion and inhibiting glucagon secretion (only glucagon-like peptide 1) receptor agonists in a glucose-dependent manner, are able to reduce hyperglycaemia with virtually no hypoglycaemic risk.

Finally, thiazolidinediones, i.e. pioglitazone, are insulin-sensitizing agents that improve glycaemic control without causing hypoglycaemia. However, as weight gain, fluid retention,[64] and heart failure have been reported with these drugs,[65] as well as concerns about increased susceptibility to fractures,[66] their use is limited in older patients.

Systemic corticosteroids are involved in 1.8–13.5% of drug-related admissions[10-12,28,29,31,56] and might cause gastrointestinal haemorrhages, deep or superficial venous thrombosis and, more commonly, hyperglycaemia.[11,12,29,56,67] An increased risk of pneumonia has been consistently observed with inhaled corticosteroids[68] used in long-term therapy of chronic obstructive pulmonary disease to reduce the incidence of exacerbations, particularly with fluticasone.[69]

3.3 Cardiovascular Drugs

This group includes several drugs, i.e. antihypertensive medications (diuretics, angiotensin-converting enzyme inhibitors [ACE-Is], angiotensin II type 1 receptor blockers [ARBs], β-blockers, α-blockers, calcium antagonists), nitrates, digoxin and anti-arrhythmic agents, statins.

ADEs caused by this drugs class are thought to be responsible for 9.8–48.4% of drug-related hospitalizations.[11,16,19,29,55] Across studies, diuretics seem to be the main drugs involved, with a percentage ranging from 1.1 to 27% of drug-related admissions.[10-12,16,19,28-31,55,56] Syncope and electrolyte disturbances (mainly hyponatraemia and hypokalaemia), together with hypotension, dehydration (with or without acute renal failure), and gout are the main clinical manifestations of diuretic-related ADEs leading to hospitalization.[11,12,19,29,56,67] Thiazide-associated hyponatraemia (and hypokalaemia) is a particularly prevalent problem in elderly people, especially in those who are concomitantly treated with ACE-Is[70] or other drugs, e.g. selective serotonin reuptake inhibitors (SSRIs). Diuretics are also responsible for drug-related falls leading to hospitalization.[71]

ACE-Is account for 2.9–13.9% of drug-related hospitalizations,[11,12,16,19,28,29,55,56] being responsible for hypoglycaemia, fall/syncope with or without hypotension (and dizziness), hyperkalaemia, renal failure, cough and angioedema.[11,12,20,29,56,67] The concomitant use of ACE-Is/ARBs and diuretics with non-steroidal anti-inflammatory drugs (NSAIDs), usually low-dose aspirin, known as 'the triple whammy', can precipitate acute renal failure, hyponatraemia or hyperkalaemia, especially when used in elderly or dehydrated individuals, and the risk is associated with the number of these drugs.[72]

ADEs caused by β-blockers are thought to be responsible for approximately 6–9% of drug-related hospital admissions,[11,12,16,28,29,55,56] presenting mainly with syncope, bradycardia, advanced atrioventricular blocks or other arrhythmias, as well as hypotension and hypoglycaemia.[11,12,29,56,67] Importantly, digoxin alone accounts for 2.9–9.7% of drug-related hospitalizations,[10-12,16,19,28,29,55,56] with a range of clinical presentations, including bradycardia, syncope, advanced atrioventricular blocks, torsades de pointes and other arrhythmias, nausea/vomiting, constipation.[11,12,19,29,56,67]

Calcium antagonists are thought to be responsible for 4.2–10% of ADE-related admissions,[11,16,29,55] presenting with syncope or hypotension, bradycardia, atrioventricular block and other arrhythmias (especially non-dihydropyridine compounds), as well as gastroduodenal lesions with bleeding and severe constipation.[11,29]

Finally, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are effective in the secondary prevention of cardiovascular events (stroke, myocardial infarction and death) also in older patients. The US National Cholesterol Education Program Adult Treatment Panel III guidelines recommend that older people should not be denied the benefits of cholesterol-lowering therapy that are offered to other age groups,[73] despite oldest old patients (>80 years) possibly having a higher risk of muscle toxicity.[74]

3.4 Analgesic Drugs

As the majority of older adults experience pain, either due to acute or chronic diseases and disturbances, analgesic drugs, including NSAIDs, opioids and acetaminophen, are often prescribed in this population. Analgesic drugs have been found to be responsible for 6.2–17.8% of ADE-related hospital admissions, mainly caused by NSAIDs.[12,28,31,55]

Clinically, the main ADE caused by NSAIDs is gastroduodenal bleeding,[11] whose risk is increased in older patients.[75] Despite the lower hospitalization rate for gastrointestinal bleeding, an increased risk of unstable angina and myocardial infarction has been reported with COX-2 inhibitors.[76] Moreover, stroke, renal and/or heart failure have been reported with NSAIDs.[12,67,77] NSAIDs are responsible for worse renal function by impairing renal perfusion through the inhibition of prostaglandin synthesis; their effect is often reversible on drug withdrawal but nephrotic syndrome and chronic kidney failure are possible, depending on dose and exposure.[77,78] Concomitant renal disease, hypovolaemia due to diuretics as well as other concomitant drugs (i.e. ACE-Is or ARBs, see above) contribute to increase the risk of acute renal failure.

As a result of the increasing awareness of NSAIDs side effects, recent guidelines on the treatment of persistent pain in older adults have increasingly advised to reduce their use and favour acetaminophen and opioids, which are, however, not without safety issues.[79]

Acetaminophen is still recommended as first-line therapy for pain in older adults. However, its overdose, often unintentional, is the most common cause of acute liver failure, even severe and fatal, and is a frequent cause of hospitalization, particularly in the USA.[80] Acetaminophen toxicity can also produce renal failure, particularly with a high dose taken for many years.[81] The main causes seem to be the use of acetaminophen in multiple products, including over-the-counter medicines[80,82] and the inadequate knowledge about acetaminophen toxicity.[83]

Opioid analgesics account for 1.8–6% of drug-related hospitalizations in older people.[12,28,31,67] Respiratory depression is the most serious side effect, which can quickly become life threatening. Other common adverse reactions with opioid use include constipation, nausea/vomiting, central nervous system (CNS) effects (sedation, hallucination,

confusion, impaired judgement and psychomotor function), and falls. Moreover, these drugs have a distinct potential for abuse.[84]

The use of opioids has increased in recent years and their indications have extended from cancer pain to different types of non-cancer pain, often treated with long-acting or extended-release formulations. Although it is acknowledged that opioids can improve persistent pain, their long-term effectiveness is not clearly established and they have potential risks. Therefore, they should be used by providers who are knowledgeable on the pharmacology of these drugs and are willing to monitor carefully patients who are treated.[79,84,85]

3.5 Central Nervous System-acting Drugs

This group includes several drugs, i.e. benzodiazepines, antidepressants (tricyclic agents, SSRIs, etc.), antipsychotics (conventional or atypical), antiepileptic and mood-stabilizing agents (e.g. valproic acid and lithium) and anti-parkinsonism and antidementia compounds.

ADEs caused by this drug class are thought to be responsible for 3.6–20.5% of drug-related hospitalizations,[16,19,28-31,55] with a wide range of clinical manifestations that are partly similar for all these drugs. Altered mental status (delirium/confusion, coma), falls and syncope (with or without orthostatic hypotension), gastrointestinal (bleeding, constipation) and respiratory disturbances (respiratory distress, pneumonia) and neuropsychiatric or other neurological symptoms,[12,19] together with hyponatraemia[12,86,87] have been more frequently reported.

Falls constitute a leading cause of injuries, hospitalization and deaths among older adults. Psychotropic drug use has been consistently associated with falls.[71,88] The landmark systematic review and meta-analysis performed by Leipzig et al. in 1999,[89] updated by Woolcott et al. in 2009,[90] showed that users of sedatives and hypnotics, antidepressants (SSRIs conferring a higher risk than tricyclic agents or trazodone, and also being associated with a significant decrease in bone density and a double risk of fragility fractures),[91] both short and long half-life benzodiazepines, and both typical and atypical, despite fewer extrapyramidal side effects, antipsychotic agents caused an increased risk of falls,[71] in keeping with a further study by Bloch et al.[92] The risk of falling generally increases with the dosage and duration of administration, but the first weeks after a new prescription also carry a higher risk.[71] Similarly, anticonvulsant drugs (even when used as mood stabilizers or in the management of behavioural and psychiatric symptoms in older patients with dementia) and anti-parkinsonism agents (it is unclear if independently of the high risk of falling of the underlying disease) have been associated with a higher risk of falling.[71] Finally, the 'anti-cholinergic load' of drug therapy has recently been associated with falls and hospitalizations in institutionalized and community-dwelling elderly patients, respectively.[93,94]

Psychotropic-induced hyponatraemia may have serious clinical consequences, such as delirium, seizures and rhabdomyolysis, and is a risk factor for neuroleptic malignant syndrome.[87] Newer antidepressants, including SSRIs, serotonin–norepinephrine reuptake inhibitors, selective noradrenaline reuptake inhibitors and noradrenergic and specific serotonergic antidepressants can all cause hyponatraemia, mainly by inducing the inappropriate secretion of antidiuretic hormone (ADH),[95,96] similar to some anti-epileptics (i.e. carbamazepine and oxacarbamazepine). In contrast, the mechanism by which antipsychotic drugs induce hyponatraemia is still unclear. It is generally thought that antipsychotics (both typical and atypical) stimulate ADH release in the brain and/or enhancement of the activity of ADH on the kidney, although it has also been suggested that both typical and atypical antipsychotics might induce severe polydypsia by stimulating the thirst centre or by causing a dry mouth.[87]

Atypical antipsychotic agents (mainly olanzapine and risperidone) have recently been associated with a slight but significant increase in the risks of death[97] and stroke[98] in patients with dementia, leading the US Food and Drug Administration to release a black box warning.[99] Subsequently, conventional antipsychotic agents have also been found to confer an increased risk of death,[100] stroke[101,102] and sudden cardiac death due to arrhythmias.[103,104] However, it is

still controversial whether antipsychotic agents also increase the risk of myocardial infarction.[105-107] Concerns about safety should be emphasized even more taking into account that an increased long-term risk of mortality has been found in patients with Alzheimer's disease who continue antipsychotic agents compared with those whose treatment is discontinued.[108]

Furthermore, antipsychotic drugs have been consistently associated with the risk of community-acquired and aspiration pneumonia.[109,110]

Cholinesterase inhibitors and memantine are commonly prescribed in older adults to treat dementia. The use of cholinesterase inhibitors has been associated with increased rates of syncope, bradycardia, pacemaker insertion and hip fracture.[111,112] A recent meta-analysis has confirmed that cholinesterase inhibitors may increase the risk of syncope, with apparently no effects on falls, fractures and accidental injury, although the number of adverse events was quite small and lower than expected, suggesting the presence of under-reporting.[113]

Finally, lithium is commonly used to treat bipolar affective disorder, also in the elderly. Drug–drug interaction with diuretics (which promote renal sodium wasting), ACE-Is (which reduce glomerular perfusion pressure), or NSAIDs (through a mechanism involving interruption of renal prostaglandin synthesis) can enhance the tubular reabsorption of lithium, predisposing to toxic effects at the CNS and kidney level.[114] The risk of hypothyroidism, hyperparathyroidism and weight gain are also increased with lithium therapy.[115]

4. Mechanisms of Adverse Drug Events Leading to Hospitalization

Age-related pharmacokinetic and pharmacodynamic changes are likely to play a role in the higher incidence of ADEs in older individuals.[116,117] The decline in renal function, which occurs in the majority of older people, seems to be an important determinant of the increased susceptibility to ADRs, particularly for hydrophilic drugs[118,119] and CNS agents.[117]

Women appear to be more susceptible to ADRs compared with men,[120] but the causes are presently unclear. In some individuals, genetic predisposition plays an important role in the occurrence of ADRs.[121]

Polypharmacy (usually defined as taking five or more drugs daily) has been consistently shown to be associated with a higher probability of ADRs,[4,122] but some authors have suggested that the use of unnecessary or inappropriate medications is the true risk factor for ADEs.[122-124] In addition, multimorbidity, i.e. the presence of multiple diseases in a single person, is another cause of the higher probability of ADRs in older patients.[17,125] It is likely that both drug–drug and drug–disease interactions can account for a large part of the polypharmacy effect on ADRs:[54,126,127] the most common drug–drug interactions are warfarin–NSAIDs or aspirin, amiodarone–digoxin, amiodarone–phenothiazines and β-blockers–verapamil,[128] while the most common drug–disease interactions are aspirin and peptic ulcer disease, calcium antagonists and heart failure and β-blockers and diabetes.[129]

Polypharmacy and/or multimorbidity might also be a marker of ill health, frailty and geriatric syndromes.[130] Frailty is a peculiar condition of older people, with a lower homeostatic capacity leading to greater vulnerability and clinical instability, meaning that drugs are more likely to produce undesired effects due to the weakening of physiological counteracting mechanisms, and also that medicines useful in a certain clinical condition might easily become harmful when such a clinical situation changes.

An important contributing factor to the high prevalence of ADEs in older individuals is the persistent exclusion of older people with multiple comorbid illnesses, disability and who are taking several drugs from clinical trials.[131,132] This situation prevents providers who prescribe drugs to 'real world' older patients from knowing the efficacy and particularly the safety profile of these drugs.

Medication errors (inappropriate prescription or administration, inadequate surveillance or monitoring) are also an important cause of ADEs. Inappropriate drug prescription is defined as a prescription in which the risk of adverse events caused by the drug outweighs the clinical

benefits, in particular when there is a safer and effective alternative therapy.[133] In the past two decades, several reports have shown a high prevalence of inappropriate drug prescription among older patients, independently of whether they were community-dwelling,[134] hospitalized,[135] nursing home residents[136] or using home-care services.[137] Inappropriate drug prescription is thought to represent an important cause of ADRs/ADEs[138] and medication-related hospitalization,[139] and might therefore become a major target for reducing the incidence of ADEs.[140] However, two different methods have been used to define inappropriate prescription:[141,142] (1) The explicit method, based on prespecified criteria, e.g. the Beers criteria and the Screening Tool of Older Persons' Prescriptions (STOPP) and the Screening Tool to Alert Doctors to Right Treatment (START) criteria. The former, developed in the early 1990s in North America[143] and repeatedly revised,[144-146] consist of two lists of medications to be avoided in older people, independently of diagnosis and considering diagnosis; the latter, recently developed and validated in Europe.[147-149] (2) The implicit method, which is more complex and time consuming, as it requires a thorough evaluation of each pharmacological therapy by a qualified professional, e.g. the medication appropriateness index, an implicit 10-item index of drug prescription quality.[150] Use of the STOPP and START criteria allowed the identification of a higher number of drugs, which are potentially used in an inappropriate way and increase the risk of avoidable ADEs that contribute to hospitalization compared with the Beers criteria,[151] and their implementation in clinical practice was demonstrated to allow a reduction in the extent of inappropriate prescription.[152]

An emerging area of interest is related to the role of the lack of or inadequate monitoring as a cause of ADEs.[153] As the estimate of the risk/benefit profile of a drug is often not reliable in the individual patient, many events are very difficult to predict in advance, and the only mechanism that might protect patients from experiencing harmful consequences is an appropriate monitoring of the pharmacological therapy. Even if the original prescription might have been appropriate, it commonly happens in older patients that an adverse event arises during the course of treatment and if this event is not detected early and interventions are not adopted to mitigate it, it can lead to severe clinical consequences, including hospitalization.[153] Monitoring might imply different activities, depending on the pharmacological therapy involved, e.g. performing regular clinical visits to evaluate the occurrence or the changes in signs and symptoms that might be caused by drugs as well as requesting laboratory examinations or diagnostic procedures. In older patients with multiple diseases and taking multiple drugs, monitoring becomes even more important than in younger adults, but several studies have shown that it is often overlooked or not performed properly in clinical practice.[154] The relevance of monitoring becomes clear when considering that less than 25% of ADEs have been shown to be preventable at the prescription stage,[154-157] which means that they are not related to errors, including inappropriate prescription, but are the consequence of properly prescribed therapies, i.e. they are ADRs. Drugs requiring regular monitoring represent the most common cause of hospitalizations as a result of ADEs.[19,21,154-157]

In some instances monitoring is performed but its interpretation is incorrect, e.g. the providers fail to recognize symptoms reported by the patient or laboratory abnormalities as being caused by some drugs or when they recognize this connection but do not reduce the dose or discontinue the offending drug.[155,156,158,159] In two prominent reports, failure to respond appropriately to patient-reported symptoms accounted for 63% of ameliorable ADEs in one study, whereas failure to act on available clinical and laboratory information accounted for 37% of preventable ADEs in another.[155,156]

Moreover, medication errors leading to ADEs and hospitalization can also occur in drug transcribing, dispensing and administering: indeed, errors at the medication administration stage account for 26% of all serious medication errors.[160] Two hospital-based studies have found that 11.5–19% of medication administrations contain an error, and 3.1–7% of the administration errors have the potential to cause patient harm and can

be considered potential ADEs.[161,162] A recent study highlighted that many medication errors occur in a domestic setting. Approximately 97% of medication errors are as a result of drug administration errors (comprising a double dose, wrong dose, wrong medication, wrong route and wrong time), whereas pharmacist dispensing errors accounted for 2.26% of errors.[163] Finally, patient non-adherence to therapy should be considered. It is well known that adherence is low for chronic conditions and, indeed, approximately 50% of older adults do not adhere to at least one of their chronic medications.[164]

Concerning non-adherence in general, although few data are available, it seems that at least one third of drug-related hospital admissions in the USA are a consequence of non-adherence.[3,165] Preliminary data recently showed that 5% of unplanned hospitalizations would be caused by therapeutic failures and 1% by drug withdrawals,[166] a sign of poor adherence, in keeping with some other previous studies.[28,167,168]

Several factors might be responsible for non-adherence: polypharmacy, regimen complexity (number of daily doses of a medication, non-oral routes of administration, the need for specific dosing instruction, e.g. warfarin), therapeutic failures and side effects, as well as disease (depression and cognitive impairment reduce adherence, clinical picture, e.g. lack of symptoms or long asymptomatic phases might undermine compliance), patient (age, cognitive and socioeconomic status, sensory limitations, disability that prevents patients from using some drugs, health literacy, etc.), health system (costs, formulary substitutions, prior authorization, fragmentation of care, limited access to healthcare professionals) and provider (multiple providers/multiple prescribers, proper education of patient and his/her caregiver) factors.[3,169,170]

5. Prevention

In view of the relevant morbidity, mortality and healthcare costs caused by ADE-related hospitalizations, every effort should be taken to reduce their occurrence.[64,171,172] High quality education on the principles of geriatric medicine and clinical pharmacology of older adults is fundamental for medical students as well as continuous medical education for providers who prescribe medicines to older persons.[173] Besides the attention to the principles of appropriate prescription, greater attention should be devoted to the other factors associated with the occurrence of ADEs, in particular monitoring of pharmacological therapies, whose relevance is often underappreciated.[153]

Several steps should be consistently adopted in order to reduce the possibility of ADEs. First, in clinical practice, a thorough medication review, including recent variations and patient adherence, is of paramount importance but is often difficult to obtain. In this context, specific attention should be paid to prescribed drugs and over-the-counter drugs and herbal medicines,[174] and to a previous history of ADRs.[175]

A careful history and physical examination should always be performed in order to obtain a likely diagnosis before prescribing any drugs.

Providers should limit the prescription to drugs that have a favourable risk to benefit ratio in each patient, choosing, among different medicines available for that disease, the safest and best known medication, always considering the individual patient comorbidities (i.e. chronic kidney and/or liver disease, and any other disease that can interact with the prescribed drug) and preference.[140] When available, a pharmacological therapy that can decrease the risk of adverse events due to another specific drug, e.g. proton pump inhibitors that reduce the risk of gastrointestinal bleeding caused by NSAIDs,[176] should be considered.

When deciding on drug prescription it is of paramount importance to take into account the overall life expectancy of the patient and his/her degree of frailty.[177]

The time that is needed should be devoted to perform a thorough education of the patient and the caregivers, for example by informing them how to take the medication correctly and also about the first potential symptoms and signs of an ADE, but without frightening them.[67,170]

Some recent reviews evaluated the existing evidence concerning interventions able to reduce inappropriate drug prescription[178] and improve

prescribing in older adults.[124,129] While there is mixed evidence for educational interventions performed on providers in the framework of continuing medical education,[178] more positive results have generally been reported with the use of computerized decision support systems,[179] pharmacist interventions[124,180] and comprehensive geriatric assessment implementation in clinical practice.[178,181] A promising intervention seems to be the systematic use of explicit criteria to detect inappropriate prescribing, in particular the STOPP and START criteria.[152] However, even if several studies have shown a reduction in inappropriate drug prescription, they have usually failed to demonstrate a reduction in ADEs.

As many errors occur at the stage of order transcription or administration, it has been proposed that the use of healthcare information technology could be helpful to prevent such events. The available evidence, mainly collected in the hospital setting, does support the use of computerized physician order entry[182] and bar code technology[161] as effective strategies to reduce medication errors.[172] Future studies should evaluate the efficacy of technology in other settings, e.g. nursing homes and home care, as a means to reduce ADE-related hospitalizations.

Whenever possible, non-pharmacological therapies should be used and unnecessary medications should be stopped. The monitoring of prescribed drugs and the reassessment of ongoing medications provides an invaluable opportunity to tailor pharmacological therapy to the current needs of the older patient as well as to detect ADEs at an early stage, before they can cause more severe clinical consequences.[67,154] New insights into this context are expected from an ongoing trial.[183] Moreover, the physician should try as much as possible to avoid prescribing new medicines to treat the side effects of current therapies, a phenomenon that is known as the prescribing cascade.[159] Indeed, the withdrawal of drugs commonly implicated in ADRs, such as cardiovascular and psychotropic drugs, is feasible and, in some studies, was associated with a reduction in potentially drug-related negative events.[184,185]

The presence of cognitive impairment or dementia should always be considered as it might significantly reduce adherence to treatment,[186] as well as sensory deficits and disabilities that can impair the ability to take medicines as prescribed. In complex older patients, it is not surprising that comprehensive geriatric assessment might be an effective method of reducing inappropriate prescription,[181,187] although the effect was not consistently significant,[188] probably because of the heterogeneity of comprehensive geriatric assessment interventions across studies.

Having one physician who is primarily responsible for each complex risk patient and improving communication among different health providers and with patients is also a crucial point.[67,189] Medication reconciliation aims to ensure that medications are not added, omitted or changed inadvertently during care transitions. It requires a coordinated effort of several professional groups (i.e. providers, pharmacists and nurses), and can be conducted using medical records either on paper or electronically.[190] There is some evidence that medication reconciliation facilitates drug therapy monitoring and reduces discrepancies between medications that have the potential to cause ADRs in older hospitalized patients.[191,192] More research is needed to test the hypothesis that medication reconciliation reduces the risk of ADRs in different settings and patient groups, for example, patients with dementia in long-term care facilities.

An innovative approach for the prevention of ADRs was recently proposed by Onder et al.,[193] who developed and validated in a large multicentre European dataset (Gerontonet) a score to identify older patients at an increased risk of ADRs. The number of drugs, history of ADRs, renal disease, liver disease, congestive heart failure, comorbidity, defined as the presence of at least four chronic diseases, were all risk factors for the occurrence of ADRs. Although this score has not been shown to predict ADEs in other prospective studies,[194] further work is needed in this potentially relevant field.

Finally, optimizing patient adherence is a further objective to be pursued in order to reduce ADE-related hospitalization in older adults. Multifaceted interventions (involving verbal and/or written patient education combined with behavioural in-

terventions and/or provider-focused components in the form of a medication review) have been shown in the general population to enhance medication adherence for long-term treatments.[164,170,195] In older adults, there is some evidence concerning the effectiveness of educational interventions and, more consistently, of the use of memory aids and cues in improving adherence,[196] but the effect of this improvement on clinical outcomes is still uncertain.[164]

6. Conclusions

ADE-related hospitalizations in older people are a public health problem. While the epidemiology and risk factors for the occurrence of ADEs have been well characterized in the past few decades, interventions to reduce their occurrence have only recently been evaluated. The adoption of sound principles of drug prescription, reduction of inappropriate prescribing, adoption of state of the art technology, monitoring of ongoing therapies, involvement of a pharmacist in the team, implementation of comprehensive geriatric assessment and interventions to maximize patient adherence are all promising strategies. However, their use in routine clinical practice is still far too limited, and future research should focus not only on increasing the evidence base for existing and new interventions but also on how to promote their implementation in clinical practice.

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