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Adverse drug reactions in special populations – the elderly

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The International Conference on Harmonization considers older people a 'special population', as they differ from younger adults in terms of comorbidity, polypharmacy, pharmacokinetics and greater vulnerability to adverse drug reactions (ADRs). Medical practice is often based on single disease guidelines derived from clinical trials that have not included frail older people or those with multiple morbidities. This presents a challenge caring for older people, as drug doses in trials may not be achievable in real world patients and risks of ADRs are underestimated in clinical trial populations. The majority of ADRs in older people are Type A, potentially avoidable and associated with commonly prescribed medications. Several ADRs are particularly associated with major adverse consequences in the elderly and their reduction is therefore a clinical priority. Falls are strongly associated with benzodiazepines, neuroleptics, antidepressants and antihypertensives. There is good evidence for medication review as part of a multifactorial intervention to reduce falls risk in community dwelling elderly. Multiple medications also contribute to delirium, another multifactorial syndrome resulting in excess mortality particularly in frail older people. *Clostridium difficile* associated with use of broad spectrum antibiotics mainly affects frail older people and results in prolonged hospital stay with substantial morbidity and mortality. Antipsychotics increase the risk of stroke by more than three-fold in patients with dementia. Inappropriate prescribing can be reduced by adherence to prescribing guidelines, suitable monitoring and regular medication review. Given the heterogeneity within the older population, providing individualized care is pivotal to preventing ADRs.

Introduction

In the United Kingdom, nearly a quarter of the population will be aged over 65 years by 2034. The most rapid increase has been in the numbers of 'oldest old' (those aged 85 years and over). It is projected that by 2034 there will be a 2.5-fold increase in the numbers of oldest old, who will then constitute 5% of the population [1]. As a consequence, health services are increasingly required to meet the needs of an ageing, often multimorbid population [2, 3].

What makes the elderly a 'special' population in pharmacological terms?

The International Conference on Harmonization considers older people a 'special population', as they differ from younger adults in terms of comorbidity, polypharmacy, pharmacokinetics and greater vulnerability to adverse drug reactions [4].

Multimorbidity

Multimorbidity refers to the co-occurrence of two or more medical or psychiatric conditions, which may or may not directly interact with each other within the same individual [5].

A systematic review of 39 studies which attempted to measure the prevalence of multimorbidity in a primary care setting found 95.1% of people aged 65 years and older were multimorbid [3]. Similarly, in a cross-sectional study of 1.7 million people registered in primary care in Scotland, the prevalence of multimorbidity was 81.5% in people over 85 years of age [6].

The prevalence of the most common conditions in the multimorbid in a Scottish study of primary care patients aged over 75 years were hypertension 61.9% (95% CI 61.5, 62.3), ischaemic heart disease 31.2% (95% CI 30.9, 31.5), pain 23.6% (95% CI 30.9, 31.5), chronic kidney disease 18.5% (95% CI 18.2, 18.7). Depression, diabetes, constipation, stroke, thyroid disease and hearing loss made up the rest of the top 10 most prevalent conditions [7].

The increase in multimorbidity in older people leads to increased prescribing in this population. Polypharmacy increases the risk of drug interactions and adverse events [8]. Individual older people can vary greatly from others of a similar age in terms of health, disability and physiologic reserves [9]. This observed heterogeneity makes the development of separate chronic disease management guidelines for older people potentially inappropriate.

Practice guidelines are often drawn from the results of clinical trials from which frail, older and comorbid people have been excluded [10–12]. The extrapolation of evidence from younger, healthier and physiologically different populations to older people make it difficult to predict reliably the prevalence and nature of adverse drug events that can be expected in 'real world' usage [13].

Modern medicine is based on evidence based interventions. Health care is driven and commonly audited against standards and protocols derived from research into single disease states. The over-reliance on guidance concerning management of single disease states systematically disadvantages people with more than one health problem by potentially promoting fragmented and poorly coordinated care that is not tailored to the person's individual health status, health risks or personal treatment priorities, resulting in inefficient, ineffective and potentially harmful treatment. In 2004 the United Kingdom introduced a payment by results system into primary care as part of the Quality and Outcomes Framework. This system allowed up to 25% of a primary care physician's salary to depend on participation and fulfilment of standards defined by single disease guidelines. This led to an increase in protocol driven, often nurse led management of chronic diseases in primary care [14].

It is difficult to develop guidelines that deal with multimorbidity. The British Geriatrics Society and NICE [15] have declared intentions to develop guidelines that consider multimorbidity. Guidelines for the management of diabetes in frail elderly issued by the American Geriatrics Society and the European Working Party in diabetes could be a model for including multimorbidity in treatment guidelines [16, 17]. Tight glycaemic control needs to be maintained for at least 8 years in order to avoid diabetic vascular complications [18], which means people in the last decade of life have limited benefits from such a strategy. Additionally, there is evidence of increased mortality in older people with tight glycaemic control [18], and recurrent hypoglycaemia can contribute to the development of dementia [19]. Consequently, guidelines advocate prioritization of goals of care and recommend more permissive targets for glycaemic control for frail older people with limited life expectancy.

Age related changes in pharmacodynamics and pharmacokinetics

Ageing is associated with physiological changes that affect how medicines are handled, including alterations in volumes of drug distribution, metabolism and clearance which can prolong half-life, increase potential for drug toxicity and the likelihood of adverse drug reactions [20]. In addition, elderly patients may have altered drug responsiveness, due to reduced homeostatic reserve in different organ systems e.g. the risk of orthostatic hypotension is greater in older people prescribed vasodilators, because of attenuated baroreceptor responses.

The main contributors to altered pharmacokinetics are age related changes in organ mass and blood circulation along with changes in body composition. A reduction in liver size of 25–35% [21] and a decrease in hepatic blood flow of more than 40% are seen in healthy ageing [22, 23], resulting in reduced drug clearance. Reduced hepatic size and blood flow also contribute to reduced first pass metabolism, which is relevant when considering the potential for increased bioavailability and adverse drug events for drugs with high hepatic extraction that undergo significant first pass metabolism e.g. propranolol.

The glomerular filtration rate (GFR) is significantly affected by disease states common in the elderly e.g hypertension and heart failure. Cross sectional studies have shown a steady deterioration in renal function with ageing although it is likely that studies are confounded by disease [24]. A 1989 cross sectional study of healthy people over a range of ages, including 10 people aged over 61 (median age 70) years demonstrated GFR was only slightly lower in elderly normotensive individuals with normal dietary protein intake than in healthy younger controls [25]. In spite of these findings, pragmatically kidney mass and blood flow have been observed to decline throughout adult life resulting in a 40% reduction in available nephrons by the eighth decade of life [25].

Age related reductions in renal function affect the clearance of drugs predominantly eliminated by the kidney e.g penicillins, diuretics and digoxin. Serum creatinine is commonly used to estimate renal function in practice. However, creatinine alone is not an adequate measure of renal function in older patients with reduced muscle mass [26]. Estimating creatinine clearance from the Cockcroft–Gault equation is a more appropriate way to estimate kidney function, especially in frail older people with low body mass.

Age related changes in body composition contribute to altered drug distribution [27]. The relative decrease in total body water with age results in a smaller volume of distribution and therefore higher serum concentrations for water soluble drugs (e.g. alcohol, gentamicin). Likewise, the higher proportion of body fat seen in ageing can prolong the half-life for fat soluble drugs like diazepam and amitryptiline.

Vulnerability to adverse drug reactions

Adverse drug reactions (ADRs) are common in elderly people in community, residential care and hospital

settings. In an Irish retrospective cohort study of 931 community dwelling people over 70 years (mean age 78 years, range 70–98 years), 674 (78%) people were established by self report and clinician review as having experienced at least one adverse drug event during the 6 month study period (95% CI 0.78, 0.98) [28]. A prospective cohort study of long term care residents of nursing care facilities in Massachusetts found 410 adverse drug events in 2916 study participants (14.06%) over a 12 month period [29].

A Dutch cross sectional study of hospital admissions due to ADRs in patients over 70 years admitted to general medical wards, found 25 out of 106 patients were admitted due to an adverse drug event (23.6%) [30]. In contrast, a prospective Italian study of 1756 patients aged over 65 years (mean 76.5 ± 7.4 years, range 65-93 years) admitted to a geriatric inpatient setting, found 102 (5.8%) had been admitted due to an ADR [31].

Studies investigating ADRs as a cause of hospital admission have produced a wide range of estimated rates of admission due to adverse drug events. Many studies contain relatively small numbers of participants. A sizeable proportion of the studies available are now 20 to 30 years old and may not reflect modern prescribing practice. The observed variance is contributed to by the inclusion of different age ranges, different admission settings (dedicated geriatric unit *vs*. general unselected medical intake), and the study methods employed to define and identify ADRs. A large, prospective study of 18 820 hospital admissions, found 6.5% of admissions were the result of an adverse drug reaction (95% CI 6.2%, 6.9%). This study included all adult admissions (>16 years), and is likely to underestimate the incidence found in an exclusively older population [32].

Risk factors for ADRs in older people

There is evidence that ADRs are more common with increasing age. In a prospective observational study of 18 820 patients admitted to a general hospital in the United Kingdom, patients admitted with ADRs had a median age of 76 years (IQR 65–83) in contrast to patients without ADRs, median age 66 years (IQR 46–79), 95% CI 8, 10 years [32]. In a study of ADRs in hospital inpatients from the same study group, the median age of patients experiencing an ADR was 72 years (IQR 56–81) compared with a median age of 61 years in those without ADRs (IQR 41–77) [33].

In a Scottish study of 1011 elderly people (over 65 years) screened for drug related problems by a pharmacist on admission to hospital, the incidence of possible or definite drug related problems was 14.2%, 5.3% were classified as precipitating hospital admission. The mean age of patients with drug related problems (78 ± 6.9 years) was significantly greater than that of patients without them (76.2 ± 7.2 years) [34].

A number of factors other than age itself are likely to contribute to this excess risk. Older age is frequently accompanied by polypharmacy, comorbidity and frailty with decreased physiological reserves. In a US study of nursing home residents, Field *et al*. found adverse drug events were more likely in residents with higher comorbidity scores, in those recently admitted to nursing home and in those taking more than five medicines [29].

Polypharmacy has been consistently identified as a risk factor for adverse drug events. The risk of ADRs increases from 13% in a person taking two medicines to 58% when taking five and 82% when taking seven or more [35]. Field *et al*. found the number of regular prescribed medications correlated with risk of adverse drug events, those taking five to six medicines OR 2 (95% CI 1.2, 3.2), seven to eight medicines 2.8 (95% CI 1.7, 4.7) and nine or more medicines OR 3.3 (95% CI 1.9, 5.6), respectively [8].

Frailty, defined as 'A medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death' [36], increases in prevalence with advancing age. Nursing home residents tend to be frail with a high burden of disease and poor functional level. Additional decrements in drug metabolism have been well described in frail older people compared with fit older people [37–39].

Common drugs involved in ADRs in older people

The majority of ADRs in older people are Type A reactions i.e. they are attributable to a predictable known pharmacological effect of a drug. Type A adverse drug reactions are usually avoidable and typically involve commonly prescribed medications [13, 40].

In a study of Irish Community dwelling older people, the most common adverse drug events were bleeding or bruising associated with warfarin and aspirin, dyspepsia related to NSAID use and dizziness or unsteadiness with psychotropic drugs [28].

In a North American study of adverse drug events in nursing home residents, those who received particular drug categories were at excess risk of a preventable adverse event. These drug classes were antipsychotics OR 3.4 (95% CI 1.2, 5.9), anticoagulants OR 2.8 (95% CI 1.6, 4.7), diuretics OR 2.2 (95% CI 1.2, 4) and anti-epileptic medications OR 2 (95% CI 1.1, 3.7). In total, 39% of all adverse events were categorized as serious or possibly life threatening; and 42.9% of these were thought to be preventable compared with 18.7% of adverse drug events categorized as significant but not serious enough to be fatal or life threatening [41].

A systematic review of nine studies of ADRs as a cause of hospitalization, found 51% of preventable drug related admissions were associated with antiplatelet agents (16%), diuretics (16%), NSAIDs (11%) or anticoagulants

(8%) [40]. In a prospective Italian study of 1756 consecutively admitted patients aged over 65 years, 45.1% of ADRs were classified as definitely avoidable and 31.4% as potentially avoidable [31].

The nature of ADRs in older people

ADRs can be difficult to identify. A particular challenge is that ADRs commonly present as symptoms or problems already prevalent in older people e.g. dizzy spells, falls or confusion [42]. It is easy for the physician to overlook the possibility of an ADR, resulting in a drug cascade where one drug is used to treat the adverse effect of another.

The term 'geriatric syndrome' is used to capture those clinical conditions in older persons which are by their nature non-specific and do not fit into a single deficit diagnosis. Geriatric syndromes presenting acutely in older people (delirium, falls, dizziness, urinary incontinence) have been identified as particular targets for medication rationalization. In a North American study of 1247 long-term care residents, the most common manifestations of an adverse drug event were delirium, oversedation and falls [43].

Falls

The prevention of falls is an important clinical target in the management of older people. Fall-related injuries are associated with significant subsequent morbidity, decline in functional status, increased likelihood of nursing home placement and greater use of medical services. Even when falls are not associated with serious injury, the risk of institutionalization is increased, partly due to loss of confidence leading to functional decline [44–47]. The importance of preventing falls is emphasized by older people themselves. An Australian study found 80% of older (>75 years) women preferred death to a 'bad' hip fracture that would result in nursing home admission [48].

It is estimated that approximately one in five falls require medical attention. However less than one in 10 results in a fracture [49]. Approximately 70 000 to 75 000 hip fractures occur each year in the United Kingdom, the majority of which are a result of falls in older people. About 10% of people with a hip fracture die within 1 month and about one-third within 12 months. Most deaths are due to associated conditions rather than the fracture itself, reflecting the high prevalence of multimorbidity in this patient group [50].

Polypharmacy is associated with increased falls risk, and medication review forms part of the multifactorial intervention recommended for older people who fall. Psychotropic and cardiovascular drugs are among the medications most commonly associated with falls. In a meta-analysis of 22 studies of medication use and falls, falls risk increased with the use of hypnotics or sedatives (OR 1.47, 95% CI 1.35, 1.62), neuroleptics and antipsychotics (OR 1.59, 95% CI 1.37, 1.83), antidepressants (OR 1.68, 95% CI 147, 1.91), benzodiazepines (OR 1.57, 95% CI 1.43, 1.72) and antihypertensives (OR 1.24, 95% CI 1.01, 1.50) (see Table 1) [51]. There is also evidence that withdrawing these medications can reduce the incidence of falls in older people [52].

Delirium

Delirium occurs in 10–31% of medically unwell hospital inpatients. It is associated with increased length of hospital stay, increased mortality, poor functional and cognitive recovery, increased likelihood of discharge to residential care and earlier onset of dementia [53].

The aetiology of delirium is multifactorial. Polypharmacy and inappropriate prescribing are risk factors for delirium, and may be the precipitating cause in 12–39% of cases [54]. Even medications that have previously been well tolerated can provoke delirium in the context of acute illness. In a North American study of hospital in-patients, adding more than three medications the 24–48 h before a delirium episode was a risk factor for delirium [55].

Although uncontrolled pain is itself a risk factor for delirium, the use of opioid analgesics is also a risk factor; accounting for 37% of all medication induced delirium in one small study of medical inpatients aged over 70 years [56]. A systematic review of drugs associated with delirium identified opioids (OR 2.5, 95% CI 1.2, 5.2), benzodiazepines (OR 3, 95% CI 1.3, 6.8), dihydropyridine calcium channel blockers (OR 2.4, 95% CI 1, 5.8) and antihistamines (OR 1.8, 95% CI 0.7, 4.5) as common precipitants (Table 2) [57].

Table 1

Medications that increase the risk of falls

Medication class	Level of evidence [51]
Hypnotics and sedatives	Level II (3 cohort, 3 cross sectional, 1 case control)
Neuroleptics and antipsychotics	Level II (3 cross sectional, 1 cohort, 1 case control)
Antidepressants	Level II (4 cross sectional, 2 cohort, 3 case control)
Benzodiazepines	Level II (4 cross sectional, 4 cohort, 3 case control)
Antihypertensives	Level II (3 cohort, 2 case control, 1 cross sectional)

Table 2

Medications that increase the risk of delirium

Medication class	Level of evidence [57]
Opioids	Level II (3 cohort)
Benzodiazepines	Level II (5 cohort, 1 cross sectional)
Calcium channel blocker	Level III (1 cohort)
Antihistamines	Level II (1 cohort)

Some adverse drug events deserve particular attention given their severe outcomes in older people. These include *Clostridium difficile* infection as a complication of the use of broad spectrum antibiotics, and the increased mortality and stroke risk associated with antipsychotics in patients with dementia.

Clostridium difficile infection

The incidence, morbidity and mortality associated with *Clostridium difficile* infection (CDI) has increased in Europe and North America over the last decade. The increase in severe and recurrent cases has coincided with the spread of hypervirulent strains, particularly the NAP1/PCR-ribotype (RT) 027 strain [58].

CDI disproportionately affects older people and those with multiple comorbidities. Older people are more likely to suffer serious consequences of infection including organ failure, recurrent CDI and death. Gut flora can be altered in older people and the immune response to infection is attenuated by age and malnutrition [59].

The pathogenesis of CDI is complex but the association of *C. difficile* diarrhoea with antibiotic use is well established. The use of antibiotics permits *C. difficile* overgrowth and predisposes to infection. Approximately 90 % of cases occur during or up to 8 weeks following antimicrobial treatment [59].

Prescription of proton pump inhibitors (PPI) in hospital is associated with increased risk of *C. difficile* diarrhoea (OR 1.78, 95% CI 1.47, 2.85) [60]. The co-prescribing of proton pump inhibitors (PPI) with antibiotics is associated with an approximately two-fold increased likelihood of infection (OR 1.96, 95% CI 1.03, 3.70) above that observed with PPI alone. Recurrent CDI is associated with PPI use (OR 2.51, 95% CI 1.16, 5.44).

A UK study of PPI prescriptions in 138 hospitalized patients diagnosed with CDI over a 4 month period, found 63 % of PPI users who suffered infection did not have valid indications for PPI use [61]. The UK department of health guidance on *C. difficile* recommend that the indications for starting a PPI or continuing a prescription be critically reviewed in patients at risk of CDI [62]. In patients who require an acid suppressing agent, histamine$_2$ receptor antagonists could be considered as they have a lower risk of CDI (OR.071, 95% CI 0.53, 0.97) compared with PPIs.

Antipsychotic use in people with dementia

Antipsychotic drugs are commonly used for behavioural and psychological symptoms in dementia. These features are common affecting up to 90% of dementia sufferers during the course of their illness [63]. Antipsychotics in this population are associated with increased risk of falls (OR 2.24, 95% CI 1.24, 4.08), oversedation (OR 2.38, 95% CI 1.76, 3.20 with risperidone), parkinsonism (OR 1.83, 95% CI 1.00, 3.36), cerebrovascular events (OR 3.64, 95 % CI 1.72, 7.69) and death from all causes (OR 1.54, 95% CI 1.06, 2.23) [63].

A systematic review of 16 randomized, double-blind, placebo controlled trials of atypical antipsychotics in the management of aggression and psychosis in Alzheimer's disease found significant improvement in psychosis with risperidone and aripiprazole, and small improvements in aggressive symptoms with olanzapine and risperidone. However, risperidone, in particular, was associated with significant increased risk of cerebrovascular events (OR 3.64 *vs*. placebo) [63].

In his 2009 report 'time for action', Banerjee estimated that 180 000 of the 700 000 people with dementia in the United Kingdom were receiving antipsychotic medication. Of these it is likely that approximately 36 000 people may have derived some benefit from treatment, however, at a cost of as many as 1620 additional cerebrovascular events, and 1 800 excess deaths per year in addition to what would be expected in this generally elderly population [64]. This report recommended that reducing the number of prescriptions for these drugs be made a clinical governance priority throughout the NHS [64].

The National Dementia & Antipsychotic Prescribing Audit 2012 showed a 51.8% reduction in the number of people with dementia receiving a prescription for antipsychotics from 2008 to 2010. However it is likely that a degree of inappropriate prescribing persists [65].

Preventing adverse drug reactions in clinical practice

Inappropriate medications are defined as 'medications or medication classes that should generally be avoided in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available' [66]. In a study of 1106 nursing home residents in North America, 40% of participants were prescribed at least one inappropriate medication as defined by Beers' criteria [66].

General measures to promote good prescribing in older people and to prevent adverse drug events include the careful identification and documentation of diagnoses, medication and previous ADRs. Drug doses should be titrated carefully from a low starting dose and patients actively monitored for the development of adverse effects. New symptoms in older people should be considered as possible ADRs, to prevent the spiral of polypharmacy.

Medicines reconciliation

Medication reconciliation is particularly important at times of transitions in care when prescribing errors are high [67]. In a prospective study of newly admitted medical inpatients receiving at least four regular medicines, 81 of 151 eligible patients (53.6%, 95% CI 45.7%, 61.6%) had at least one unintended prescription discrepancy. The most common error (46.6%) was omission of a regularly prescribed medication [68].

A systematic review of 26 studies, including 10 randomized trials, found medication reconciliation consistently reduced discrepancies, with a decrease in actual and potential adverse drug events [69].

Consider non-prescription medication

Patients should be routinely asked about 'over the counter' or alternative medicines they may be taking in addition to their prescribed drugs. Alternative or 'herbal' medicines may cause or contribute to adverse drug events.

One study of 3072 ambulatory adults aged 75 years or older in the United States found 82.5% of the study cohort used at least one dietary supplement, with 54.5% using three or more [70].

Healthcare staff may not enquire about the use of alternative medicines and supplements and patients may not volunteer this information. In one North American telephone survey, 34% of the study cohort admitted to taking at least one unconventional drug, and 72% of this number reported that they did not inform their clinician that they were using them [71].

Examples of herb–drug interactions include *Ginkgo biloba* augmenting the anticoagulant effect of warfarin and St John's wort taken with serotonin re-uptake inhibitors, increasing the risk of serotonin syndrome in older adults [72]. Herb-induced alteration in cytochrome P450 enzymes is the most common mechanism implicated in these interactions.

Alternative medicines and their indications, although not at present evidenced by good quality clinical trials, along with their potential for interaction with conventional medicines are listed in Table 3 [73–83].

Consider potential for patient related errors

Patient related errors can contribute to adverse drug events. In a study of 30 000 Medicare enrolees aged over 65 years followed for a 12 month period, 99 adverse drugs events (23.5% of all adverse drug events) and 30 potential adverse drug events (13.6% of potential adverse drug events) were attributed to patient error [84]. The most commonly implicated drug categories were hypoglycaemics, cardiovascular drugs, anticoagulants, non-opioid analgesics and diuretics. Patient errors mostly occurred in medication administration, failure to follow clinical advice and autonomous modification of medication schedules. Patient factors that increase risk of errors include cognitive impairment and mental illness along with poor vision and physical dexterity. Errors are more likely in patients with complex medication regimes. Blister packs provide a potential method of overcoming some of these issues, along with consolidation of drug dosing schedules and providing clear, written instructions to patients about their prescriptions [84].

Medication review

The National Service Framework for Older People recommends that patients aged 75 years and over should have their repeat medicines reviewed annually and those on four or more medicines twice yearly, enhancing communication between different healthcare providers with greater involvement of pharmacists in prescribing advice

Table 3

Common indications and interactions of alternative medications

Alternative medication	Indications [73, 74]	Interactions
St John's Wort	Depression	Antidepressants (selective serotonin re-uptake inhibitor, monoamine oxidase inhibitor) [75] Warfarin [76] Digoxin [77] Statins [78] All cytochrome P450-metabolized agents [79]
Asian Ginseng	Promote wellbeing Erectile dysfunction Hypertension Diabetes	Can lower blood glucose; potential interaction with hypoglycaemic agents [73] Inhibition of platelet aggregation, reduced platelet adhesiveness [73]
Gingko biloba	Dementia Intermittent claudication Tinnitus	Increased bleeding tendency [73, 80] Warfarin/NSAIDS/Heparin
Kava	Anxiety, insomnia	Can provoke dystonia Dopamine agonists/antagonists CNS depressants [73, 81]
Saw palmetto	Benign prostatic hypertrophy	Increased bleeding tendency Anticoagulants Antiplatelets [73, 82, 83]

and supporting patients and carers to improve concordance and compliance [85].

'Brown bag reviews' when patients are asked to bring all their medications, including over the counter and alternative medicines to an appointment with a community pharmacist, have been well established in the United States for some years. A study of brown bag reviews with 205 patients (mean age 64.45 years) in 23 pharmacies in South East London resulted in pharmacist interventions in 87% of reviews. Pharmacist interventions included improving patient knowledge about the purpose of their medication (65% of reviews), improving or correcting usage (46%), identifying interactions between prescribed medications and over the counter drugs (4%), identifying non or poor compliance with at least one medication (58%). 14% of all reviews led to the patients' GPs being notified and 12% of reviews exposed potential for hospital admission due to ADR or non-compliance [86].

Despite the potential of medication review to maximize benefit from prescribed medications and reduce ADRs, at present there is no strong research evidence for its effectiveness in improving clinical outcomes. A systematic review of the effectiveness of medication review in hospital inpatients found no significant effect on mortality or hospital readmissions [87]. Another systematic review of interventions to optimize prescribing for older people in care homes concluded that there is some evidence that medication appropriateness is improved but no evidence that ADRs, hospital admissions or mortality are reduced [88].

Reducing polypharmacy

Tackling polypharmacy is a particular challenge in elderly people with multiple chronic diseases. A recent King's Fund report concludes that much could be done to improve appropriateness of prescribing by using medications that have good evidence for their usage, and avoiding drugs that are not clinically indicated or are unlikely to be effective [89].

Each of the main four cardiovascular prognostic drug classes (aspirin, ACE inhibitors, β-adrenoceptor blockers and lipid lowering treatments) reduce the relative risk of future vascular events by approximately 25% when prescribed in isolation. The cumulative effect of all four drugs along with lifestyle modification and blood pressure management could theoretically yield very beneficial returns. However in 'real life' use the returns are less impressive and each additional drug provides a smaller risk reduction [90]. This diminishing return is important when considering the efficacy of multiple medications for a number of chronic diseases. Concentration of prescribing on important medications with greatest proven benefit and omitting others has the potential to limit polypharmacy and reduce ADRs in clinical practice [90].

Consider therapeutic aims

It is important to consider overall therapeutic aims particularly when prescribing for frail older people vulnerable to ADRs [91, 92]. When considering therapeutic goals for patients late in life, attention should be paid to remaining life expectancy, time until treatment benefit, goals of care and treatment targets [91, 92]. The risk: benefit ratio of each medication should be reviewed in turn. There is evidence that many patients with a known terminal illness and limited life expectancy continue to take medications for secondary prevention and treatment of chronic disease until death, increasing the likelihood of ADRs and potentially adding morbidity to the last phase of life [93].

Use of prescribing indicators

Prescribing indicators can be used to define and detect potentially inappropriate medications in older people.

Beers' criteria developed in the USA [94] and the Irish STOPP (Screening Tool of Older Person's Prescriptions) criteria [95] are two of the most widely cited. Both have been developed by consensus expert opinion based on reviews of primary research evidence. The advantages of using the STOPP criteria in UK practice are that they include drugs in widespread use in Europe and are more sensitive to potentially inappropriate medicines than the Beers' criteria [96]. STOPP can be used in tandem with START (Screening Tool to Alert doctors of Right Treatments). START criteria comprise 22 indicators of potentially important prescribing omissions in older people [97].

There is evidence that STOPP criteria identify potentially inappropriate prescribing and can improve the quality of prescribing in community and acute settings. A recent retrospective cohort study of 931 community dwelling patients in Ireland (aged $>$70 years) found a prevalence of potentially inappropriate prescribing of 42%. Patients who had more than two potentially inappropriate prescriptions identified by the STOPP tool were more likely to have experienced an ADR (OR 2.21) and were more likely to attend A&E [28]. There is a lack of evidence for beneficial effects on mortality and quality of life [98, 99].

Computer based systems

Computer based systems have the potential to alert clinicians to possible drug interactions or errors. These systems are already in widespread use in primary care in the United Kingdom and are being introduced to inpatient care settings [100].

There is evidence mainly from North America that these systems can reduce inappropriate prescribing for older people in different care settings. In a study of potentially inappropriate prescribing in older ambulatory care patients, computer generated alerts were conveyed to prescribing physicians by telephone by pharmacists, resulting in a rate of change to a more appropriate agent

of 24% [101]. A study performed at a North American hospital investigating the use of a computer system that alerts a prescriber to prescription errors, displays relevant guidelines, suggests dosing, frequency and possible alternative medications demonstrated significant improvements in prescribing behaviour [102]. Most of the research that has been conducted in this area has focussed on processes that may lead to ADRs, and not on actual patient outcomes [103].

In a cluster randomized controlled trial, 1118 long term care residents in the United States were randomized to prescriptions being processed by an electronic system alone (controls) *vs.* an electronic system with a clinical decision support tool (intervention). Rates of total ADRs and preventable ADRs were similar in both intervention and control groups. The clinical decision support tool produced 2.5 alerts per resident month, 50% of which were probably unnecessary which may have led to prescribers disregarding alerts [104]. This has also been identified in other studies. It is estimated that 49%–96% of alerts provided by clinical support decision tools are overridden or ignored [105].

Prescribing indicators and tools should not be used in isolation. Good clinical judgement and an understanding of the patient's overall condition and personal treatment goals remain pivotal to providing high quality individualized care and preventing ADRs.

Conclusion

Prescribing for older people is challenging. Multimorbidity and polypharmacy are common increasing the risk of adverse drug events, with reported prevalence of ADRs in community dwelling older people as high as 78% [28], incidence in a care home population of 1.89 per 100 resident-months [29] and precipitating between 5.8% and 23.6% hospital admissions in older people [30, 31]. It is difficult to strike the right balance between ensuring good access to potentially beneficial treatments and protecting patients from inappropriate prescribing and potential harm. This challenge is compounded by the under-representation of older people and those with co-morbidities in clinical trials.

Pharmacokinetics alter with ageing and drug doses often need adjustment to avoid adverse drug events. Regular medication review, potentially aided by prescribing indicators or electronic prescription systems, can help optimize prescribing and the benefits patients get from their medicines. Good communication between healthcare providers, patients and carers is key to managing medicines well.

Clinicians who look after older people should maintain a low threshold for considering an adverse drug reaction as a cause or contributor to medical illness, especially where presentation is non specific in nature.

Competing Interests

Both authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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