

Drugs and the older person

Multiple pathology often means multiple medication in the older person.

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Persons aged 60 years and over are the main consumers of drugs because of increased pathology requiring multiple medications. No local data are available but USA data show that while older persons constitute 13% of that country's total population, they consume approximately 35% of all medications used.¹ Ageing alters pharmacokinetics (absorption, distribution, metabolism and elimination) and pharmacodynamics (drug-receptor or drug-organ interactions), which affects choice, dose and dosing frequency of many drugs. Pharmacological and non-pharmacological factors associated with ageing predispose older persons to an increased risk of adverse drug events. Knowledge of drug therapeutics is based on studies in younger people, as older persons are largely excluded from drug trials; adverse drug events in the older population are therefore only identified in the post-marketing phase. Adverse drug events are observed 2 - 3 times more frequently in older than in younger adults² and account for 5 - 17% of hospital admissions in this age group.³

Age-associated mechanisms of altered drug effects

Changes in pharmacokinetics and pharmacodynamics that occur with age result from changes in physiological function. In addition, multiple chronic diseases and consequent polypharmacy increase drug-drug and drug-disease interactions.⁴ Changes in homeostasis such as decreased plasma volume and thirst mechanism, diminished vasomotor regulation and impaired glucose tolerance decrease compensatory mechanisms and increase susceptibility to adverse drug reactions.⁵

Drug absorption

Age-related changes lead to a decrease in small-bowel surface area and an increase in gastric pH, but these changes do not lead to clinically significant changes in drug absorption.⁶ Factors affecting drug absorption include patients' comorbid illnesses, timing of drug administration and other accompanying products. An increase in gastric pH from proton pump inhibitors or antacids may decrease absorption of certain drugs, such as imidazole antifungals and ampicillin, and increase the absorption of nifedipine and

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amoxicillin.^{7,8} Most drugs are absorbed from the gastrointestinal tract by simple diffusion and there are no age-related changes in the absorption of these drugs. Drugs absorbed into the blood stream via active transport mechanisms (iron, calcium, magnesium and vitamin B₁₂) are poorly absorbed in the elderly.⁹ Intestinal metabolism and active extrusion of absorbed drugs have recently been recognised as a major determinant of oral drug availability and contribute to poor oral bioavailability of certain drugs. Cytochrome P450 (CYP) 3A, the major phase I drug metabolism enzyme and a multi-drug efflux pump, P-glycoprotein, are present at high levels in small-intestinal enterocytes.¹⁰ These proteins are induced or inhibited by many compounds. P-glycoprotein inhibitors, e.g. ketoconazole and atorvastatin, increase bioavailability of digoxin, and administration of rifampicin, a potent inducer of CYP3A and P-glycoprotein, decreases the bioavailability of cyclosporin and nifedipine.¹⁰

Drug distribution

Ageing results in changes in body composition with increased adipose tissue and decreased total body water and lean body mass. These changes lead to an increased volume of distribution of lipid-soluble drugs. Thus, lipid-soluble drugs, e.g. chlorthalidone, diazepam, amiodarone and verapamil, are excreted from the body at a slower rate, prolonging the half-life,^{8,11} and taking longer to reach a steady-state concentration, i.e. the amount of drug entering the system being equal to the amount being eliminated. Water-soluble drugs, e.g. cimetidine, digoxin, ethanol and lithium, have a decreased volume of distribution, leading to a higher plasma concentration. Certain drugs bind to plasma proteins and their pharmacological effect is determined by the unbound proportion of the drug. Poor nutrition, chronic illness and debility lead to decreased serum albumin.¹² Highly protein-bound drugs, e.g. warfarin, non-steroidal anti-inflammatory drugs (NSAIDs), phenytoin, valproic acid, diazepam, lorazepam, calcium channel blockers and proton pump inhibitors have elevated free and pharmacologically active drug concentrations, leading to a higher incidence of drug toxicity.^{1,8,11}

Age-related changes lead to decreased liver size, hepatic blood flow and enzyme activity.

Drug metabolism

The liver is primarily responsible for drug metabolism and the kidney for drug excretion, but metabolism can also take place in the intestinal wall, lungs, skin, kidneys and other organs. Age-related changes lead to decreased liver size, hepatic blood flow and enzyme activity.¹³ A decrease in hepatic blood flow prolongs the duration of effect in drugs that undergo extensive first pass metabolism, e.g. propranolol, theophylline, tricyclic antidepressants, verapamil and nitrates – less drug is extracted, increasing bioavailability.⁷ Drug metabolism occurs either through phase I reactions: oxidation, reduction, hydroxylation, dealkylation and hydrolysis, which are mediated through the cytochrome P450 (CYP450) enzyme system or phase II reactions. Cytochrome P450 enzymes are found primarily in hepatocytes and cells of the wall of the gut. The phase I drug metabolism pathway, which leads to biotransformation of a drug to a more polar product for excretion, is decreased in elderly persons, increasing free drug concentrations and potential toxicity. Examples of drugs that undergo phase I metabolism are diazepam, chlordiazepoxide, codeine, diphenhydramine and warfarin.^{2,11} Drugs that either inhibit or induce this enzyme system may predispose to drug interactions with toxicity or under-treatment. Phase II reactions, unaffected by age-related changes, involve conjugation of drugs through glucuronidation, acetylation or sulphation; examples of drugs that undergo phase II metabolism are lorazepam and oxazepam.⁶

Drug excretion

Most drugs are eliminated by the kidney as either the parent compound or as a metabolite or metabolites. Glomerular filtration declines as a consequence of a decrease in renal blood flow and kidney size and a decrease in functioning nephrons.⁷ Serum creatinine in an older person is not an accurate reflection of renal function. An older person's production of creatinine is reduced due to a decline in lean muscle mass.⁸ Measurement of 24-hour creatinine clearance would be the most accurate way of determining the dosage of renally excreted drugs, but is time consuming and requires an accurate 24-hour urine collection. The Cockcroft and Gault equation, although it has limitations, can be used to estimate a patient's creatinine clearance in the absence of renal failure:

$$\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{body weight (kg)}}{0.82 \times \text{serum creatinine } (\mu\text{mol/l})}$$

For females, multiply serum creatinine by 0.85 instead of 0.82.

Renal excretion of drugs depends on glomerular filtration rate (GFR). GFR decreases by 10% per decade from the age of 30, though these changes are not universal. With ageing, both glomerular filtration and tubular secretion of drugs are reduced. Elimination of a drug is affected by reduction in renal function if 60% of the drug is renally excreted.⁵ Renally excreted drugs, e.g. allopurinol, aminoglycosides, penicillin, atenolol, sotalol, angiotensin-converting enzyme (ACE) inhibitors, digoxin, H₂ blockers, lithium, metformin, require dose adjustment and monitoring.¹¹ Toxicity may also result from combining two drugs that compete for renal secretion, e.g. probenecid and penicillin. Serum drug levels may be used to monitor certain drugs but drug levels within therapeutic range, e.g. toxicity of digoxin, do not exclude clinical toxicity.

Pharmacodynamics

The pharmacodynamic action of a drug is the length and intensity of its pharmacological effect on target cells. In older patients, changes in drug-receptor or drug-organ interactions cause changes in drug effect. Ageing causes many receptors to function less efficiently and reduces the density of beta receptors, leading to toxic reactions from beta blockers, such as propranolol and diminished response to β_2 -agonists, such as salbutamol.^{8,11} A decline in parasympathetic control increases the effects of anticholinergics, e.g. urinary retention, blurring vision and constipation. A reduction in brain receptors, an increase in blood-brain barrier permeability and a decrease in cerebral blood flow increase brain sensitivity to drugs; delirium, sedation, depression and confusion are commonly associated with anticholinergics, antidepressants, analgesics, neuroleptics, digoxin and anticonvulsants.^{2,11} In addition, a progressive reduction in homeostatic mechanisms predisposes the elderly to toxic reactions, e.g. postural hypotension in response to drugs that lower arterial blood pressure.² Advanced age is a risk factor for developing sulphonylurea-induced hypoglycaemia because of impairment of glucose counter-regulation.²

Polypharmacy

The balance between therapeutic gain and risk becomes critical in the elderly. Drug-drug interactions increase exponentially with the number of drugs used. Polypharmacy provides an opportunity not only for drug-drug interactions but also drug-disease interactions.¹⁴ Examples of drug-disease interactions are anticholinergic drugs (amitriptyline, clomipramine and dothiepin), which exacerbate glaucoma, benign prostatic hyperplasia, dementia and xerostomia (dry eyes), and NSAIDs, which exacerbate hypertension and cardiac failure.¹¹ The presentation of adverse drug events is nonspecific, which increases a tendency to treat adverse events with other drugs.

Under-prescribing of beneficial medications to older adults is equally prevalent. Under-prescribing may result from avoidance of over-prescribing, adverse effects or complex medication regimens, as well as from a belief that older adults will not benefit from medications intended as primary or secondary prevention or from aggressive management of chronic conditions such as hypertension or diabetes mellitus. Commonly under-prescribed medications include ACE-inhibitors and β -blockers for heart failure, aspirin following an acute myocardial infarction, warfarin for atrial fibrillation, statins for primary prevention of cardiac events, and narcotic analgesics for pain control.⁷

Adverse drug events

An adverse drug event is defined as an injury resulting from the use of a drug at usual doses. While some drug reactions are idiosyncratic (type B reactions) and thus unpredictable, 65 - 70% occur because of known pharmacological effects (type A reactions) and are mostly avoidable. Adverse drug reactions have been estimated to account for 7.9 - 24% of all hospitalisations of elderly patients.³ Risk factors for adverse drug events are listed in Table I. Table II shows common modes of presentation of adverse events in the elderly from commonly used drugs.

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Table I. Risk factors for adverse drug events in older patients⁷

- Age > 85 years
- Low body weight or body mass index
- ≥ 6 concurrent chronic diagnoses
- Estimated creatinine clearance < 50 ml per minute
- ≥ 9 medications
- ≥ 12 doses of medications per day
- A prior adverse drug reaction

Table II. Common presentations of adverse drug effects in the elderly¹⁵

Adverse effect	Drug group
Confusion	Benzodiazepines, phenothiazines, anticholinergic agents, tricyclic antidepressants, antiparkinson agents, narcotic analgesics, anticonvulsants, corticosteroids, theophylline (if toxic), digoxin (if toxic), NSAIDs (less often), cimetidine (less often)
Gait disorder	Benzodiazepines, phenothiazines, butyrophenones, anticonvulsants
Postural hypotension	Antihypertensives, diuretics, phenothiazines, tricyclic antidepressants, antiparkinson agents
Incontinence	Diuretics, prazosin (reduced bladder neck tone), anticholinergic agents (urinary retention and overflow incontinence)
Hypothermia	Phenothiazines, barbiturates, benzodiazepines, tricyclic antidepressants, narcotic analgesics, ethanol
Constipation	Anticholinergic agents, phenothiazines, tricyclic antidepressants, verapamil

Table III. Factors predisposing to non-adherence to treatment¹

- Complexity of dosing schedule
- Frequent changes in medication or brands
- Multiple medications
- Unpleasant side-effects
- Difficult to open containers
- Cost of medication
- Difficult routes of administration
- Inadequate patient education and understanding
- Cognitive impairment
- Visual impairment
- Impairment of physical function

therapy. Special attention to these challenges may further improve drug management in older persons. Some of the challenges are listed below:

- Doctor shopping and involvement of multiple professionals, thus no health care professional takes responsibility for the care of the patient.
- Poor communication between professionals.
- Failure of patients to bring all drugs to every consultation, due to a lack of awareness of drug interactions.
- Limited doctor/patient communication due to various barriers such as language and literacy.
- Poor patient education regarding the illness and need for drug therapy.
- Use of both generic and trade names (patients may assume that they are different drugs).

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Guidelines for effective prescribing

The following precautions are required for the administration of drugs to older patients in order to avoid over-prescribing:¹¹

- Obtain a complete drug history
- Use non-drug treatment whenever possible
- Use no drug before its time and no drug beyond its time – always review the need to continue medications
- Know the drugs you use
- Start low, go slow
- Treat adequately
- Encourage treatment adherence
- Use new drugs with particular caution.

Compliance with long-term medication is especially poor as patients are not acutely ill and may not see a need for continued drug therapy. Compliance is affected by many factors but can be improved. Table III shows factors predisposing to non-adherence to treatment.

Poor compliance may be reduced by:

- simplifying drug regimens
- avoiding polypharmacy
- educating the patient and providing carefully written instructions
- warning the patient of common adverse drug reactions
- performance of cognitive and physical assessments
- encouraging face-to-face review.

Compliance

Non-compliance with a drug regimen can inhibit therapeutic response and successful treatment. Physical and cognitive impairment may prevent older patients from complying with their drug regimens. It is essential that a patient/caregiver understands why a drug is important and how to take it.

Challenges to management of drug therapy in South Africa

Health care professionals and patients are faced with specific challenges that may interfere with optimal management of drug

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In a nutshell

- Older persons may need multiple drug therapy for an increased number of chronic diseases.
- Alterations in pharmacokinetics and pharmacodynamics as well as the presence of disease and the use of multiple prescriptions and over-the-counter drugs increase adverse drug reactions.
- Substantial inter-patient variability in this age group requires individualisation of drug therapy.
- Regular review of medication, the use of simple drug regimens, maintenance of good records, patient education and ensuring good compliance are important factors in providing safe and effective therapy.
- Improved outcomes, a lower risk of adverse events, and the management or prevention of drug interactions can be achieved by applying basic principles of prescribing.

single suture

The streets are unhealthy

Prostitutes working on the streets have far more health problems than those working in massage parlours, according to a survey of sex workers in Bristol, UK. The survey also found serious gaps in the provision of health care for all sex workers, providing greater ammunition for those pushing for legalisation of brothels.

Apparently the major factor driving poor health among street sex workers is drug abuse. Only 4 of 71 massage parlour workers used heroin compared with 60 out of 71 street workers. The picture was similar for crack cocaine and other injectable drugs.

The health problems seen in greater numbers in street workers include abscesses, deep vein thrombosis, chest infections and hepatitis B and C. They were also more likely to suffer from anxiety and depression. Parlour workers experienced half the amount of ill-health reported by street workers and were more likely to be screened regularly for sexually transmitted infections.

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