Prescribing for elderly people

Ageing is associated with multiple morbidities and a subsequent need for pharmacological therapy to help control symptoms, prolong life and maintain functional independence. Changes in organ function, drug–receptor interactions and homeostasis with age can alter both drug handling (pharmacokinetics) and drug actions (pharmacodynamics). This puts elderly patients at particular risk of treatment failure, adverse drug reactions and interactions. Prescribing for these patients is particularly difficult. This article outlines some key principles that should be considered when initiating or reviewing a prescription for an older patient.

Illustrative case example

Mrs Powell is a 92-year-old woman who lives alone and independently. *Table 1* shows her daily medication regimen. She has come to the elderly care department with her daughter for an outpatient review.

Mrs Powell reports feeling dizzy while walking around the house and that she often is tired and washed out. She is fed up of taking 'all these pills' because she does not think they 'do her any good and they make her constipated'. Her daughter is concerned that Mrs Powell has become more forgetful.

Her past medical history includes anxiety, hypothyroidism, osteoporosis and osteoarthritis. Last year she had a duodenal ulcer and was treated for *Helicobacter pylori* but now has no dyspepsia. She has hypertension but no cardiovascular history.

- What changes do you think you should make to her medication?
- Does your answer change after reading the article?

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Clinical pharmacology and ageing

Pharmacokinetics

Pharmacokinetics (what the body does to a drug) is divided into absorption, distribution, metabolism and excretion. Ageing can affect all these processes, thus affecting the amount of drug that reaches the intended target – potentially reducing desired effects or increasing adverse reactions.

Absorption

Older people have delayed gastric emptying and decreased intestinal motility (Orr and Chen, 2002), which can slow drug absorption. A significant proportion of elderly patients have increased gastric pH (Hurwitz et al, 1997). This may affect the absorption of drugs that need a low pH, such as iron and calcium compounds. Drug–drug interactions within the gastrointestinal tract are a common issue in the elderly who may take multiple medications. For example oral calcium compounds reduce the absorption of drugs such as levothyroxine, iron compounds and bisphosphonates.

Table 1. Mrs Powell's drug regimen

Time		Drugs
Daily	Morning	Calcichew D3 two tablets Ramipril 5 mg Levothyroxine 125 mg Paracetamol 1 g Bisoprolol 5 mg Omeprazole 40 mg
	Lunch	Paracetamol 1 g
	Evening	Paracetamol 1 g
	Night time	Diazepam 5 mg Paracetamol 1 g
Weekly	Alendronic acid 70 mg, Friday mornings	

Important findings: weight: 45 kg (body mass index 20 kg/m^2), heart rate: 60 beats/min regular, blood pressure: lying: 165/90 mmHg, standing: 95/45 mmHg. Serum free T4 = 9.0 pmol/litre (normal range 10.0–22.0 pmol/litre); serum thyroid-stimulating hormone = 7.9 mU/litre (normal range 0.4–5.0 mU/litre)

Distribution

In the elderly, body fat is increased by up to 40% and total body water is reduced by about 10% (Beaufrere and Morio, 2000). This can alter drug distribution with clinical consequences. Water-soluble drugs, e.g. morphine, digoxin and aminoglycosides, have less body water to distribute into. This increases drug concentration and risk of toxicity, requiring a dose reduction or lower starting dose. Fat-soluble drugs, e.g. benzodiazepines, have a greater volume of distribution, leading to slower elimination, and prolonged drug action, which may require an increase in the dosing interval.

Metabolism

Drug metabolism occurs predominantly in the liver, although metabolizing enzymes are also present on the intestinal wall, kidney and lungs. It comprises two distinct phases, which convert lipid-soluble molecules (required for absorption and distribution) to hydrophilic molecules ready for excretion.

Phase 1 metabolism, predominantly by cytochrome P450 enzymes, generally reduces drug activity, although it sometimes converts inactive (pro) drugs to active metabolites (e.g. clopidogrel, enalapril). Phase 2 reactions typically conjugate drugs or phase 1 metabolites with other molecules making them inert and ready for excretion.

Hepatic changes with age, including reduced liver mass and blood flow, appear to reduce the efficacy of phase 1 reactions in the elderly (Schmucker et al, 1990). This may reduce first pass hepatic metabolism of drugs absorbed from the gut, increasing bioavailability. Subsequent reduced hepatic clearance prolongs half-life. This may increase plasma concentrations and effects of drugs that are extensively cleared by the liver, e.g. morphine and diazepam. However, co-prescription of drugs that induce or inhibit liver enzymes is more likely to be clinically relevant than age-related changes.

Excretion

Renal impairment is common in the elderly. Age-related reduction in glomerular filtration rate (<1 ml/min/year)(McLean and Le Couteur, 2004), diseases such as hypertension or diabetes, and the use of nephrotoxic

drugs, e.g. non-steroidal anti-inflammatory drugs, cause a decline in renal function. Reduced renal excretion prolongs plasma half-life and increases steady state drug concentrations of renally-excreted drugs. This may require reduced doses of drugs such as digoxin or penicillins to avoid toxicity.

Pharmacodynamics

Changes in pharmacodynamics (what drugs do to the body) associated with ageing are complex and involve changes in receptor density, signal transduction and intracellular responses (Hughes, 1998). Altered homeostatic protective mechanisms may increase the risk of adverse drug reactions.

Central nervous system

Brain mass and number of neurones and synapses decrease with age (Giusto et al, 2002), and the blood–brain barrier becomes more permeable to drugs (Pakulski et al, 2000). Adverse CNS effects of drugs (confusion, sedation and extrapyramidal changes) increase with age. Drugs with particular risk of causing CNS adverse drug reactions include opioids, benzodiazepines, anaesthetics, antimuscarinics and antipsychotics.

Autonomic nervous system

Adrenergic receptors become less sensitive with age to both agonists and antagonists. Older people experience less bronchodilation with beta-2-adrenoceptor agonists and less reduction in blood pressure from beta-adrenoceptor blockers than younger people (Connolly et al, 1995; Grossman and Messerli, 2002). Altered compensatory reflex mechanisms put elderly people at greater risk of adverse hypotensive effects of drugs, e.g. postural hypotension and increased falls risk.

Polypharmacy and undertreatment

Polypharmacy

Elderly patients comprise around 17% of the UK population but account for around 60% of community prescriptions (Information Centre (Health Care), 2008). Co-prescription of multiple medicines is termed polypharmacy, although there is no universal definition. Using the definition of 'five or more medications', the prevalence of polypharmacy was as high as 68% in nursing home residents (Vetrano et al, 2012). Taking five or more medications carries an increased risk of adverse drug reactions. Hanlon et al (1997) found that one in three patients with polypharmacy experienced at least one adverse drug reaction per year, with two thirds requiring clinical review and 11% requiring hospital admission.

Polypharmacy is also the 'use of more medicines than are clinically indicated' (Holbeach and Yates, 2010). In a retrospective study more than a third of elderly patients reviewed were prescribed potentially inappropriate medications or doses (Cahir et al, 2010). This may be because of inaccurate diagnosis, prescribing to treat symptoms caused by adverse effects of other medications or not stopping medications in a timely fashion.

Undertreatment

Undertreatment is significant and often unrecognized. In a study of 154 consecutive inpatient and outpatient geriatric patients, 31% had not been prescribed an indicated drug despite lack of contraindication (Kuijpers et al, 2008).

One reason may be that trial evidence for the use of drugs in the elderly is lacking compared to younger adults (Evans, 2011). Older people are often excluded from studies via trial design because of comorbidity, life expectancy, polypharmacy or age. This is a challenge for doctors as the population ages, with new treatments often tested only in people who are 'healthier' than those who will use medications in the real world.

Even where there is good evidence, older patients are less likely to receive drugs than younger people. For example, older patients with ovarian cancer were less likely to undergo debulking surgery or receive adjuvant or high dose chemotherapy than younger patients (Bouchardy et al, 2007). Comorbidities, reduced life expectancy and an increase in the risk–benefit ratio may contribute to undertreatment. Other factors may include nihilistic attitude of clinicians, patients and families to treatment of elderly patients as well as simple factors such as patients not physically being able to get to appointments (Gellad et al, 2011).

Adherence

Adherence is the degree to which medications are taken in accordance with the prescription made by a patient's health-care provider. While age may not be a cause of reduced adherence (Hughes, 1998), polypharmacy, cognitive impairment and functional disability are more common in the elderly and contribute to patients failing to take medicines as prescribed. Also, lack of perceptible benefit (e.g. statins), adverse effects or a lack of belief in medication may reduce adherence (Gellad et al, 2011).

Interactions

Table 2 lists commonly prescribed drugs and potential drug–disease interactions.

Table 2. Commonly prescribed drugs and potential drug–disease interactions

Drug/class		Effect on comorbid disease
Angiotensin-converting enzyme inhibitors		May exacerbate hyperkalaemia and acute kidney injury
Analgesia	Non-steroidal anti-inflammatory drugs	May exacerbate asthma, cardiac failure, chronic kidney disease
	Diclofenac, cyclo-oxygenase (COX) 2-inhibitors	Increase risk of heart disease or stroke in susceptible patient groups
	Opioid analgesia (including weak opioids like codeine)	May exacerbate constipation, cognitive impairment or dementia, falls
Anti-muscarinics	Bronchodilators, e.g. tiotropium	May exacerbate arrhythmias or tachycardia
	Bladder relaxants such as oxybutynin	May exacerbate confusion or dementia, heart failure, hypertension, hyperthyroidism, glaucoma
Benzodiazepines		May exacerbate cognitive impairment or dementia, falls, respiratory failure
Bisphosphonates		May exacerbate dysphagia, gastro-oesophageal reflux disease
Diuretics	Indapamide/bendroflumethiazide	May worsen hyponatraemia
	Furosemide	May worsen dehydration
Heparins		May exacerbate hyperkalaemia in patients with renal failure, osteoporosis (long-term effect)

Multiple medical problems and polypharmacy in elderly patients increase the risk of drug–drug and drug–disease interactions.

Authors' thoughts on Mrs Powell

Mrs Powell is prescribed 10 different medicines, several of which seem unnecessary or are not indicated. This meets all definitions of polypharmacy.

Table 3 shows the authors' comments on each drug. They would also advise that Mrs Powell is prescribed a regular laxative (e.g. senna or sodium docusate) to treat and prevent constipation.

Conclusions

Prescribing for the elderly is difficult. Changes in organ function, cell functioning and homeostasis with age mean that handling and effects of drugs are often different from those in younger patients.

Elderly patients may have multiple comorbidities and be taking multiple drugs. This, coupled with lack of age-relevant trial evidence, can make medication management in the elderly a complex task.

Good prescribing for the elderly requires an individualized patient-centred approach. When starting a new medication take a full drug history and establish comorbidities. Choose a drug with the lowest risk of interactions, that is least likely to exacerbate underlying disease. When choosing a starting dose consider weight and renal function, and use a 'start low and go slow' approach to dose titration for chronic conditions. Most importantly, age alone should not be the deciding factor in medication choice. **BJHM**

Conflict of interest: none.

Table 3. Suggested changes to Mrs Powell's drug regimen

Drug		Changes the authors would make and reasoning
Drugs with altered pharmacokinetics	Calcichew D3	Change the time when this drug is taken. It may prevent absorption of levothyroxine and interact with alendronic acid. Suggest she takes it at least 4 hours after her other medications
	Levothyroxine	No change. Changing the timing of calcium supplementation may increase absorption enough to improve her hypothyroid symptoms and biochemical picture. A symptom review should occur in the next 6 weeks with repeat thyroid function testing, at which point a dose increase could occur if needed
	Paracetamol	Reduce the dose. This could cause liver damage in a patient weighing 45 kg
	Alendronic acid	No change
Drugs with altered pharmacodynamics	Ramipril	Stop or reduce the dose. When treating hypertension in patients with symptomatic postural symptoms target the standing blood pressure (Bulpitt, 2000). Mrs Powell's standing pressure is well below that suggested for patients over 80 years of age (150/90 mmHg; National Institute for Health and Care Excellence, 2011). Either reduce her dose or change to a thiazide-like diuretic such as indapamide (if any is needed)
	Bisoprolol	Stop this drug. Beta blockers are no longer recommended as a first-, second- or third-line antihypertensive. Mrs Powell has no other indications for a beta blocker. This may also be contributing to her postural symptoms by preventing the reflex increase in heart rate on standing
Drugs with no clinical indication	Omeprazole	Stop this drug. *Helicobacter pylori* has been eradicated and she is symptom free so this drug is no longer necessary
	Diazepam	Reduce the dose gradually before stopping. Benzodiazepines cause confusion and somnolence and are only indicated for short-term treatment of severe disabling anxiety

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KEY POINTS

- Treat the physiology not the chronology.
- Avoid 'undertreatment' of patients because of their age alone.
- Avoid using more medicines than clinically indicated, to reduce the risks of polypharmacy.
- Be watchful of drug–drug interactions in patients taking multiple medications.