CHAPTER 2

Therapeutics

Medical research does not always answer physicians' dilemmas. Subgroups of patients, such as the elderly, are often not adequately represented in trials to be sure that results are also applicable to them. Trials may even specifically exclude this age group,[1] so evidence-based medicine may not support some common prescribing practices in the elderly. The other side to this is that by not prescribing certain treatments, elderly people may be unfairly denied therapies that work at least as well within their age group. There is evidence to suggest that many older people are not on treatments that are of proven benefit, such as aspirin for ischaemic heart disease and angiotensin converting enzyme (ACE) inhibitors in heart failure.[2] Therefore, the geriatrician has to tread a careful path between the potential negative effects of both polypharmacy and unreasonable under-treatment.

There is a further difficulty that confronts all physicians. The design and reporting of many drug trials is influenced by the drug company that will benefit from subsequent marketing. The potential conflict of interest is quite obvious. Perhaps more disturbingly, a number of authors of clinical guidelines are in receipt of grants from, or hold shares in, pharmaceutical companies.[3]

PHARMACOKINETICS

Generally speaking, elderly patients absorb medications similarly to younger individuals. The main differences in the pharmacokinetics occur with drug distribution and elimination. The concentration of albumin in the blood does not change significantly with ageing in the absence of severe illness. Therefore, protein binding is not usually altered. But the body composition does change as people age. Older individuals have a higher proportion of body fat, and a lower proportion of body water, than younger people (*see* p. 9). This affects the volume of distribution (Vd) of drugs (the theoretical volume of fluid that would account for the observed plasma concentration). It is increased for lipophilic drugs and reduced for hydrophilic ones. Sarcopenia may also result in a reduced Vd for drugs that bind to muscle. As the half-life of a drug is proportional to its Vd divided by clearance, a larger Vd can increase a drug's half-life. Examples of drugs with longer half-lives in the elderly for this reason include benzodiazepines and barbiturates.[4] Similarly, a reduced

clearance may have an additional effect. Permeability of the blood–brain barrier also appears to increase with advanced age, potentially increasing the risk of cognitive effects of medications.

The two main mechanisms of drug elimination are metabolism in the liver and excretion via the kidneys. Both of these are impaired in older age. The reduced hepatic metabolic capacity may be related to several processes, including reduced blood flow or enzyme activity. However, an age-related reduction in liver mass appears to be the most important factor.[5] The liver mass has been found to reduce by 20% to 50% by the time people reach 80 years of age.[6]

The glomerular filtration rate (GFR) also progressively declines with advancing age. On average this is in the order of a 10% reduction per decade after the age of 30, due to a number of physiological changes (*see* p. 12). This is taken into account in calculations to estimate GFR such as the Cockcroft-Gault formula:[7]

$$\frac{(140 - \text{age})(\text{body weight in kg})}{72\ (\text{serum creatinine [mg/dL]})}\ (\text{multiply by 0.85 for females})$$

or the Modification of Diet in Renal Disease (MDRD) equation.[8] Digoxin is an example of a drug with a reduced renal clearance and increased risk of toxicity in the elderly.[6] Some drugs are eliminated by active excretion into the renal tubules, which also appears to be diminished in older adults.

Additionally, there may be changes in the sensitivity of target organs to certain concentrations of drugs compared to younger counterparts (pharmacodynamics). This causes either increased or decreased drug efficacies at similar plasma concentrations compared to younger people. One example is the apparent increased sensitivity of older people to psychoactive medications.[6]

So, the elderly are prone to variation in drug peak concentrations and half-lives. Altering the size of drug doses or their frequency can compensate for this.

INAPPROPRIATE MEDICATION USE

A number of medications have been adjudged to be inappropriate for use in the majority of older people due to inefficacy, unacceptable side-effects or the availability of more suitable alternatives. An example is the use of sedative hypnotics, which appear to be associated with a small increase in sleep duration (mean 25 minutes) with a number needed to treat (NNT) of 13, but have many adverse effects (e.g. cognitive impairment and falls) with a number needed to harm of just six.[9]

Benzodiazepines have few indications for use in the elderly, yet they are the most commonly prescribed of the psychotropic drugs in these people. A study found that 30% of the over eighty-fives are on such agents.[10] They are associated with an increased risk of falls (*see* p. 301), cognitive impairment and fracture-related mortality.[9,10] If their use is judged absolutely necessary then drugs with shorter half-lives and lower lipid solubility are probably safer (e.g. lorazepam or oxazepam).[4] Other

drugs often deemed inappropriate include those with anticholinergic properties.[4,11] These are discussed further on pp. 104, 119 and 251. The use of either sedating or anticholinergic drugs in older adults is associated with poorer physical and cognitive functioning.[12] Non-steroidal anti-inflammatory drugs (NSAIDs) are also associated with high rates of side-effects in the elderly and are usually best avoided.[4]

The Beers criteria were derived in 1993 by expert consensus and initially developed for use in nursing facilities. They have since been updated, with the most recent version published in 2003.[13] They contain a list of medications that are deemed inappropriate for use in older adults due to either unacceptable side-effects or the existence of more appropriate alternatives. Of course, there may be situations in some individuals where these drugs are appropriate, but they should always be given careful consideration before commencement. Table 2.1 contains a short list of commonly used medications derived from the Beers recommendations. Criticisms of the Beers criteria include the fact that the list contains a large number of drugs rarely prescribed these days (e.g. thioridazine), lacks ability to detect drug–drug interactions or duplicate prescriptions, and is not an exhaustive list of potentially inappropriate drugs in older people.[14]

Despite these recommendations, there is evidence that elderly people are commonly prescribed such agents. One study found that 24% of people 65 years or older were on at least one drug that was deemed unsuitable according to expert guidelines and 20% of these people were on two or more.[15] This appears to be worse among nursing home residents where 40% have been found to be on inappropriate drugs.[16] This value represented 7% of all prescriptions in this group. In the UK around 25% of nursing home residents are on antipsychotic medications, and around 85% of these prescriptions are inappropriate according to expert guidelines.[17,18] Many of these people are on higher than recommended doses or even multiple agents. A study of older patients (n = 597, mean age 77 years) being acutely admitted to hospital found that 32% were on at least one inappropriate medication, and in 49% of these patients the medications were felt to be contributing to their presenting symptoms.[19]

Antibiotic resistance is rising, yet the development of new antibiotic drugs is declining.[20] It is ever more imperative that these drugs are prescribed appropriately. This need must be weighed against the potential harm of giving an ineffective treatment.[21] Some antibiotics are less effective in the elderly (e.g. nitrofurantoin in those with renal impairment) and some cause more harm (e.g. aminoglycosides and nephrotoxicity). The risks of developing MRSA and *C. difficile* are also higher with some drugs (*see* pp. 402 and 273). As a general rule, when an empiric antibiotic is chosen prior to culture results, outside life-threatening infections, an agent with the narrowest possible spectrum of activity that is likely to be beneficial should be selected. When broad-spectrum antibiotics are thought initially necessary, if subsequent cultures show that a narrower spectrum agent would be equally effective, treatment should be changed. Antibiotic selection will frequently require a balance between potential benefits and harms to be made.

TABLE 2.1 Examples of medications potentially inappropriate for use in older adults.

Benzodiazepines		**Notes**
	Chlordiazepoxide	*See* pp. 104 and 301
	Diazepam	
	Lorazepam	
	Oxazepam	
	Temazepam	
Anticholinergics		
TCAs	Amitriptyline	*See* pp. 104, 118 and 251
	Doxepin	
	Orphenadrine	
	Oxybutynin	
NSAIDs		
	Indometacin	Heart failure, renal failure,
	Ketorolac	hypertension and GI bleeding
	Naproxen	
	Piroxicam	
Cardiovascular		
	Amiodarone	Multiple side-effects
	Digoxin	Increased risk of toxicity
	Doxazosin	Orthostatic hypotension (OH)
	Methyldopa	Sedation, OH
	Nifedipine (short acting)	OH
Others		
	Chlorphenamine	Confusion and sedation
	Cimetidine	Confusion
	Nitrofurantoin	*See* p. 22
	Oestrogens	*See* pp. 79 and 250

The under-prescription of appropriate medications in the elderly is also a problem. In a review of 196 outpatients (mean age 75) who took an average of 8.1 drugs each (range 5 to 17), 65% were on one or more inappropriate agents.[22] However, 64% were not prescribed medicines of known benefit (most commonly antihypertensives, antiplatelets and statins). In total 87% were either on inappropriate or not on appropriate drugs, with 42% of people in both categories.

ADVERSE DRUG REACTIONS

Adverse drug reactions may account for around 12–16% of admissions to hospital in the over-seventies.[19,23] These may be unrelated to drug doses (idiosyncratic) but most are dose-dependent, and therefore potentially preventable. For this reason it is generally preferable to use the lowest possible effective dose of a drug. Some adverse reactions may develop after a prolonged exposure; for example, tardive dyskinesia with neuroleptic agents (*see* p. 149). Therefore medications should be reviewed and withdrawn, when possible, at periodic intervals.

Adverse drug reactions appear to occur commonly in the elderly,[6] especially among those in nursing homes.[24] This probably represents the fact that elderly people are on many different agents simultaneously due to multiple comorbidities, and the changes seen in pharmacokinetics and pharmacodynamics. Studies have found that the use of three or more medications significantly increases the chance of an adverse reaction.[23,25] Of the adverse events that are potentially preventable, many are related to the use of psychoactive medications with antipsychotics being the most common offenders.[25] A recent analysis of surveillance data has found that the three drugs warfarin, insulin and digoxin accounted for 33% of hospital emergency department visits for adverse drug events in the over-sixty-fives.[26] Careful consideration of the risks and benefits is needed when prescribing these classes of medication.

Adverse drug reactions may be due to drug–drug interactions (e.g. clarithromycin inhibits the breakdown of phenytoin) or drug–disease interactions (e.g. NSAIDs may worsen heart failure). Many commonly used drugs have some degree of anticholinergic action, which is associated with harm (*see* pp. 104, 118 and 251). Older adults are at risk of being on several of these drugs simultaneously, which may have an accumulative effect on the body. Scoring systems have been developed to calculate anticholinergic drug burden in older adults, which seem to correlate with risk of adverse events.[27,28]

It has been proposed that pharmacists could be used to review medications, which may lead to a reduction in adverse events due to inappropriate prescribing or drug interactions. A study randomised 368 older hospitalised patients (mean age 87 years) to pharmacist review or standard care.[29] The pharmacists communicated recommendations to the treating physicians (75% of which were actioned). Over a 12-month follow-up period there were nine admissions related to adverse drug events in the intervention group compared to 45 in the controls (i.e. an 80% reduction). The scheme was associated with lower overall healthcare costs.

POLYPHARMACY

Polypharmacy is a term used when a patient is given multiple medications. Precise definitions vary but it is often taken as being on four or more regular medications. As people age they accumulate diagnoses and, subsequently, medications. Many conditions require two or more agents to control them, for example osteoporosis,

heart failure, hypertension and ischaemic heart disease. A study found that a sample of people over the age of 72 (mean age 81 years) were on a mean number of 2.2 medications (range 0–15).[30] In a random sample of community-dwelling people over the age of 65, 19% of men and 23% of women regularly took five or more prescription drugs.[31] When a group of nursing home residents (mean age 84 years) was assessed, they were each receiving an average number of 4.8 regular medications.[32] A further sample of people aged 65 years or over who resided in residential care or assisted living settings averaged 5.8 regular medications per person.[11]

Polypharmacy may become exacerbated by the addition of more drugs to treat adverse effects of current agents, for example the addition of a diuretic agent to reduce the leg oedema caused by a calcium channel blocker. This process is what is called the 'prescribing cascade'.[33] To try to prevent this cycle, new symptoms should always be evaluated as possible drug adverse effects and alteration of prescriptions considered.

It is not uncommon to find the co-prescription of agents that have directly opposing mechanisms of action, for example beta-blockers and salbutamol, dopamine agonists and antagonists, or furosemide and fludrocortisone. Also, a recent trend of prescribing anticholinergic agents with cholinesterase inhibitors appears to have developed. This may be true for as many as 35% of those on cholinesterase inhibitors.[34] This may sometimes be caused by the commencement of anticholinergic agents to treat urinary incontinence precipitated by the cholinesterase inhibitors.[35] Yet there is evidence that this is a harmful combination.[36]

The use of multiple agents increases the risks of side-effects and interactions, and patients' adherence to their medication regimen reduces as the number of drugs increases. A regular review of medications and their ongoing justification and safety should be undertaken whenever possible. Agents without clear benefit should be withdrawn. This often occurs at the time of hospital admission when the results of medication adjustments can be closely monitored.

MEDICATION CONCORDANCE

The old term 'compliance' is being replaced by the term 'concordance' to describe a patient's adherence to prescribed therapies. This is based on the philosophy that doctors and patients are entering into an alliance and good communication between these parties is essential to its proper functioning. The patient should not merely comply with instructions but should agree with the reasoning and be a willing participant in any treatment. An alternative term is 'medication adherence'.

Estimates of concordance rates depend on what definition is applied. The value falls among patients who are being treated for illnesses of long compared to short duration and figures between 40% and 80% have been found in clinical trials of chronic conditions.[37] There is also a reduction with increasing medication regimen complexity. Patients on once-daily medications will take them around 80% of the time, whereas those on four times daily dosing will take only 50% of their

medication.[37] Other factors that have been associated with reduced concordance include the presence of psychiatric disorders (e.g. depression and dementia), medications for conditions that cause no symptoms (e.g. hypertension) and the side-effects of drugs.[37]

The identification of patients who are not taking their medications is not always easy. Sometimes drug levels (e.g. phenytoin), physiological parameters (e.g. blood pressure) or pill counts provide a clue. Usually, patient self-reporting is relied upon. It is important not to be confrontational when enquiring about concordance, as this will tend to cause patients to over-report their taking of medications. Accepting that all patients will lapse from time to time, questions should focus on how often this occurs.

Patient education on the value of their various drugs may improve the situation but is unlikely to solve the problem altogether. A logical first step is to try to reduce the number of medications and limit the number of times they are to be taken each day. For example, a once-daily formulation could be used in place of one taken twice daily. Medication aids, as discussed below, may be beneficial in selected patients. Periodic telephone counselling by a pharmacist has been shown to increase adherence in patients on multiple drugs for chronic conditions, and to reduce associated mortality.[38]

MEDICATION AIDS

Various devices and methods of drug packaging have been designed to try to improve the concordance of elderly patients with their medications. They include multi-compartment and blister packs. They usually have individual slots for tablets to be taken in the morning, lunch, afternoon and evening and span over a one-week period. Accepted wisdom is that they are of benefit; however, this is not evidence-based. Trials that have utilised them have not shown clear benefits in improved medication concordance.[39] That said, large-sized trials assessing their use in the frail elderly have not been performed. They are often started without adequate patient assessment and as many as half of these patients may do as well without them.[40] They may dissociate the patient from their medications as they become all mixed together. They are also only suitable for some drugs. Liquids or inhaled medications cannot be dispensed this way. Other medications, such as bisphosphonates or levodopa, may need to be taken at specific times or in specific ways.

MEDICATION REVIEW

Patients' medications should be periodically reviewed. This may be part of an annual programme or in response to an illness event (e.g. at the time of admission to hospital). The process can be complex for the many reasons discussed in this chapter. A reasonable balance often has to be reached between polypharmacy and inappropriate under-prescription. This is likely to be tailored according to

individual patient characteristics and preferences. Some guidance of things to consider is given in Table 2.2.

TABLE 2.2 Guidance for performing a medication review.

Problem	Example
Is the medicine still indicated?	Some medications are only suitable for short-term use – e.g. antipsychotics for agitation in dementia.
Inappropriate medications	*See* Table 2.1.
Drug–drug interactions	Proton pump inhibitors limit the efficacy of clopidogrel (*see* p. 187).
Drug–disease interactions	NSAIDs worsen heart failure.
Antagonising medications	Beta-blockers and beta-agonists.
Co-prescription of the same class	Codeine and tramadol.
Prescription cascades	Furosemide to treat leg oedema caused by diltiazem.
Inappropriate dose or formulation	Minimal effective dose, preferably once daily.
Concordance	Does the patient want to, and are they able to, take their medication as prescribed? Consider education and medication aids.
Polypharmacy	Consider limiting medication burden to a small number of the most beneficial agents.
Inappropriate under-prescription	Are all comorbidities being treated in accordance with good practice guidance? If not, are there good reasons why (e.g. side-effects, life expectancy, patient preference, difficulty taking as prescribed, or unacceptable polypharmacy)?

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