Practical advice for prescribing in old age

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Abstract

Optimizing drug therapy is an essential part of caring for an older person. Prescribing in this group has unique challenges because of the high interindividual variability in pharmacological response and the fact that frailty, rather than age, predicts physiological responses to external stimuli. The effects of drugs and how they are handled by the body change in a number of ways with increasing age. With decreasing life expectancy, drugs used for secondary prevention might not be appropriate, particularly where their adverse effects lead to a reduction in short-term quality of life. The issue of polypharmacy is of particular concern in older people who, compared with younger individuals, tend to have more disease conditions for which therapies are prescribed. A number of drugs and combinations of drugs are particularly likely to cause harm to the older person with frailty, and these should be prescribed only where there is clear benefit. Unfortunately, the process of weighing the benefits and risks of drugs in this group is made more difficult by a paucity of directly relevant evidence. Formal criteria to identify potentially inappropriate medications have been developed, but can be cumbersome to apply and suffer from a lack of flexibility. Regular medication review is an important part of management of this patient group. Suggested strategies for this are discussed.

Keywords Efficacy; frailty; geriatric assessment; inappropriate prescribing; medication review; older adults; polypharmacy; toxicity

Key points

- Prescribing in the older person with frailty is different from prescribing in young, fit adults
- Careful consideration of the benefits and risks of prescribing and continuing to prescribe medications is necessary for this group
- Quality of life, rather than therapeutic efficacy, may be more important in people with short life expectancy
- Polypharmacy is of particular concern in older people who, compared with younger individuals, tend to have more disease conditions for which therapies are prescribed
- Awareness of particular medications that are often harmful in this group is essential for good practice

Introduction

Prescribing in the era of evidence-based medicine should be fairly straightforward: we know how many people, on average, will benefit from a drug and we know how many will come to harm. This information is synthesized in easy-to-follow guidelines and, following discussion with the patient, the appropriate therapy can be prescribed with the knowledge that good is being done. What could be simpler?

The reality is, of course, rarely so clear-cut. Even in otherwise healthy individuals, there is sufficient variability in the beneficial and adverse effects of drugs that it is often inadvisable to adhere strictly to guidelines. This variability tends to increase (and the evidence base tends to decrease) with age, such that prescribing in older people can be particularly challenging.

Old age and frailty

There is an increasing recognition that chronological age is often unhelpful in predicting how well a person will cope with a given physiological challenge. Instead, a more functional individualized approach is recommended. To this end, 'frailty' is becoming the preferred term. Frailty is described as a 'reduced ability to withstand illness without loss of function' and is what defines the specialty of geriatric medicine.

Adults who are frail lack the reserve to deal with adverse events. Even minor physical, mental and social stresses can have a big impact on health and function. Prescribing in this group needs special attention as guidelines rarely take frailty into account when making recommendations. This places adults with frailty at an increased risk of adverse drug reactions; drug–drug interactions and/or rapid deterioration if necessary medication is not reviewed and optimized.

The pharmacology of ageing

The major age-related changes to pharmacokinetics and pharmacodynamics are summarized in Tables 1 and 2, respectively. As many of these changes lead to drugs having enhanced or unpredictable effects in older people, it is usually regarded as good practice to adopt a 'start low, go slow' approach, initiating therapy at the lowest possible dose and titrating up cautiously.[1] This approach must, of course, be weighed against the possibility of continuing debility or symptoms caused by the condition the drug is intended to treat.

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Examples of pharmacokinetic changes with ageing

Drug absorption	
Changes to active transport	Reduced absorption of vitamin B_{12}, iron and calcium through active transport
Reduced dopa decarboxylase in gastric mucosa	Increased absorption of levodopa
First-pass metabolism	
Reduced liver mass and blood flow	Increased bioavailability of drugs with extensive first-pass metabolism (e.g. propranolol, labetalol) Reduced activation of pro-drugs activated in the liver (e.g. enalapril, perindopril)
Drug distribution	
Relative reduction in total body water	Reduced volume of distribution and increased serum concentrations of water-soluble drugs (e.g. gentamicin, digoxin)
Relative increase in body fat	Increased volume of distribution and longer half-life of lipid-soluble drugs (e.g. diazepam, thiopental, lidocaine)
Protein binding	
No substantial age-related changes	
Drug clearance	
Reduction in glomerular filtration rate	Reduced clearance of renally excreted drugs (e.g. water-soluble antibiotics, diuretics, digoxin, lithium)
Reduction in liver mass and blood flow	Reduced clearance of drugs with a high hepatic extraction ratio (e.g. clomethiazole, glyceryl trinitrate, lidocaine, pethidine, propranolol)

Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004; **57**: 6–14.[1]

Table 1

Selected pharmacodynamic changes with ageing

Drug	Pharmacodynamic effect	Age-related change
Diazepam	Sedation, postural sway	Increased
Diltiazem	Antihypertensive effect	Increased
	Acute PR interval prolongation	Decreased
Furosemide	Peak diuretic response	Reduced
Isoprenaline	Chronotropic effect	Reduced
Morphine	Analgesic effect	Increased
	Respiratory depression	Unchanged
Temazepam	Postural sway	Increased
Warfarin	Anticoagulant effect	Increased

Adapted from Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004;**57**: 6–14.[1]

Table 2

Goal-directed therapy

A large proportion of medication is prescribed on the basis that it will prevent some harm befalling the recipient at some point in the future. Although it is increasingly clear that secondary prevention immediately following an acute event can have a significant impact on health in the short term, particularly in the field of stroke medicine, it is also clear that prevention of problems in the long term is less valuable if the individual treated is likely to die before those problems occur. For example, if a person's life expectancy following a stroke is short, prescribing a prophylactic medication such as a statin, potentially requiring several months or years to confer a benefit, may not be considered appropriate. This is particularly the case if prescribing that medication may cause significant short-term adverse drug effects.

Similarly, in chronic conditions such as hypertension and diabetes mellitus, it may be appropriate to relax prescribing and outcome targets for older people to minimize the risk of immediate harm from treatment even though the risk of potential future complications of the disease itself may rise. This approach, which might also improve treatment adherence in the long term, is increasingly being adopted when managing individuals with a single dominant condition such as advanced dementia.

Related to this is the consideration that, as life expectancy reduces, the relative value of quality of life may increase. Clearly, this will vary on an individual basis and must be discussed with the patient, but it is often appropriate to favour interventions targeting quality of life over those aimed at improving survival and/or objective clinical outcomes.

The evidence base

In order to decide whether or not a medication is beneficial overall, it is necessary to be aware of the benefit it might provide (and the harm it may cause). However, this is made difficult in the older person with frailty by the paucity of specifically applicable evidence. It is not uncommon for clinical trials to define older people as those aged >60 years, >65 years or even, in the Cochrane review of antidepressants in older patients, >55 years old. In contrast, an increasing number of those seen in modern geriatrics services are in their ninth or tenth decades.

Where evidence exists for very old individuals, the proven benefit can differ from that seen in younger people. For example, although there is a clear reduction in *cerebrovascular* morbidity and mortality associated with the use of antihypertensive drugs in the over-80s, there is not the same evidence of benefit that is found in younger patients for *cardiovascular* and *all-cause* morbidity and mortality. While it is still relatively rare for large trials to focus on people aged >80 years, it is even rarer for one to focus on people with frailty. Indeed, many trials have explicit exclusion criteria that result in those with frailty not being recruited. In this context, one option is to extrapolate outcomes from trials in younger patients, but this should always be done with caution and can be misleading.

High-risk drugs

A number of drugs and combinations of drugs are particularly hazardous in people with frailty. Although it cannot be said that