Prescribing in older people

BACKGROUND Prescribing medications to older people is difficult due to comorbidity, limited evidence for efficacy, increased risk of adverse drug reactions, polypharmacy, and altered pharmacokinetics.

OBJECTIVE This article describes the principles underlying clinical geriatric pharmacology including approaches to evaluating the evidence for risk and benefit, and adjusting dose for age related pharmacokinetic changes.

DISCUSSION The challenge for the general practitioner is to balance an incomplete evidence base for efficacy in frail, older people against the problems related to adverse drug reactions without denying older people potentially valuable pharmacotherapeutic interventions.

The decision to prescribe

Evidence for efficacy in older people

The evidence base for prescribing to frail and older people is small and disproportionate to the level of prescribing.[1] Only 3% of randomised, controlled trials and 1% of meta-analyses are published about people over 65 years of age.[2] Older people are infrequently recruited into clinical trials. For example, 37% of all patients with acute myocardial infarctions are older than 75 years of age, yet this age group only represents 2–9% of clinical trial subjects.[1] Even in specific trials of older people, exclusion criteria may lead to atypical healthy, older subjects being studied rather than frail, older subjects.[1] Thus, much of geriatric practice with respect to drug usage is reduced to being anecdotal, and at best based on extrapolation from studies in younger patients or healthy older people. Such extrapolation of efficacy data is not always appropriate. A review of angiotensin converting enzyme (ACE) inhibitors in heart failure showed that the clinical benefit seen in younger subjects is not significant over 75 years of age (*Table 1*).[3] Likewise, a clinical trial of bisphosphonates and hip fracture found benefit in postmenopausal women aged 70–79 years of age but no significant benefit over 80 years of age in women with risk factors for falling and no measures of bone mineral density (*Figure 1a, b*).[4]

Adverse drug reactions

Although marketing and guidelines tend to focus on evidence for efficacy, general practitioners also need to consider the impact of adverse drug reactions, especially in older people. The relationship between the risk of adverse drug reactions and old age is well established.[1] Older people are four times more likely to be admitted to hospital as a result of an adverse drug reaction.[1] For every dollar spent on medications in aged care nursing facilities, $1.33 is required for the treatment of drug related morbidity and mortality. About one half of adverse drug reactions in older people is preventable by better prescribing.[1]

Polypharmacy

Polypharmacy – defined as the use of five or more medications – occurs in 20–40% of older people.[1,5] Risk factors for polypharmacy include patient age and comorbidity, however, the main risk factor is the prescribing doctor.[1]

Polypharmacy is associated with several negative outcomes. The risk of adverse drug reactions is increased 3-4-fold with adverse drug reactions occurring in as many as 81% of patients on six or more medications.[1] The risk of falling and of recurrent falls is doubled with four or more medications.[6] Medication

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errors increase from 15% with one medication to 35% with four or more medications.[5]

Balancing risk and benefit

Given the practical difficulties of studying older and frail people in randomised clinical trials, alternate mechanisms for determining risk to benefit ratios need to be considered. Cost effectiveness models have been used to balance clinical trial efficacy data with adverse effect data from observational and case control studies. For example, the benefits of anticoagulation are dramatic with a reduction in stroke of 62% with warfarin.[7] However, the risk of major bleeding is at least doubled in older people on oral anticoagulants. Cost effectiveness analysis (Markov) showed that for a patient 65 years of age with no other risks for stroke, anticoagulation generated 11.5 years of quality adjusted life expectancy, compared with 11.8 years with no therapy. At age 100 years, the results were 2.0 years and 2.1 years respectively (*Figure 2*).[7] These results suggest that in older people, the adverse effects may offset the substantial benefits. For most drugs, the GP will not have ready access to such data or analyses.

Table 1. Effects of ACE inhibitors on outcomes by age group from five trials (SAVE, AIRE, TRACE, SOLVD prevention, SOLVD treatment). The odds ratio are not significant for subjects greater than 75 years of age[3]

Age in years	Number of subjects	Deaths	Odds ratio*	95% CI	Deaths /CHF/MI	Odds ratio*	95% CI
<55	3165	495	0.76	0.62–0.93	878	0.77	0.66–0.91
55–64	4315	994	0.84	0.73–0.97	1534	0.71	0.62–0.81
65–74	4194	1227	0.75	0.66–0.86	1761	0.67	0.59–0.79
>75	1066	454	0.95	0.74–1.22	590	0.89	0.69–1.13

*Odds ratio of death/adverse event when taking ACE inhibitor vs. when not

Figure 1a. Kaplan-Meier estimates of the incidence of hip fracture in women aged 70–79 years

What dose to prescribe?

Traditionally, it has been proposed that the dosage of many drugs should be reduced in older people to compensate for the age related changes in pharmacokinetics.[8]

Age related changes in pharmacokinetics

There are age related changes in drug absorption from the gut, protein binding and volume of distribution, but the clinical implications are minimal.[1]

The hepatic metabolism of many drugs is reduced, in some cases in the order of 30–50%. This appears to be secondary to age related changes in hepatic blood flow, liver mass and the hepatic endothelium rather than aging changes to drug metabolising enzymes or their expression.[1,9,10]

It has been accepted that there is a marked age related reduction in creatinine clearance in older people, even in the presence of a normal serum creatinine. The Cockcroft Gault equation is often used to determine the creatinine clearance in older people in order to adjust the maintenance dose of renally cleared drugs with narrow therapeutic indices such as aminoglycosides, digoxin and lithium.[8] However, the Cockcroft Gault equation was derived from men with suspected renal disease, and recent studies indicate that in healthy older people, renal function is largely maintained (*Figure 3*).[1] The few studies on the effects of aging on gentamicin, digoxin and lithium pharmacokinetics have not shown any dramatic reduction in renal clearance.[1]

Rather than relying on generalisations about aging changes in liver and renal function to define dosage, regulatory authorities now require pharmacokinetic data on older people. When such data are available, it should be used to determine dosage.

Clinical implications of dosage changes

The critical issue is whether altering the dose has any implications for clinical outcomes – either safety or efficacy. There is no clinical trial evidence supporting dose reduction for any medication in older people. However, many clinicians use lower doses of medications in order to minimise dose dependent adverse drug reactions.[1]

For example, lower doses of digoxin are recom-

mended in older people to avoid concentration dependent adverse effects. Old age significantly increases the risk of toxicity even in the usual therapeutic range and toxicity in older people is unrelated to pharmacokinetic changes. On this basis it has been argued that the digoxin level should not exceed 1.4 ng/mL in people beyond the seventh decade.[1]

Although reducing dose might minimise adverse drug reactions, the converse effect on efficacy in older people is unknown. Indeed, it could be argued that in some settings higher doses of medications are required; for example high doses of broader spectrum antibiotics might be appropriate because of age related immunosuppression.

Monitoring pharmacotherapy

Because the rate of adverse drug reactions is substantial and in many cases the efficacy is uncertain, it is important to monitor older patients on drug therapy closely.

When adverse drug reactions occur in older people, they are more likely to be severe and less likely to be recognised or reported by the patient.[1] Adverse drug reactions have taken over from syphilis and tuberculosis as the great mimic of systemic disease,[11] and most geriatricians would consider adverse drug reactions as a cause for any problem in an older person, simply because they are very common and very easy to treat. Adverse drug reactions have very diverse presentations, but GPs need to be especially vigilant for falls and confusion.

The risk of falling is increased by 71% in older people taking psychotropic medications.[6] Benzodiazepines are associated with a 50–110% increase in the rate of hip fractures, and up to 10% of hip fractures among older people living in the community are attributable to benzodiazepines.[12] Confusion is frequently secondary to medications. Medications cause 11–30% of cases of delirium and 2–12% of cases of chronic confusion or dementia.[13] Although anticholinergic drugs and psychotropic drugs are common culprits, any drug should be considered.

One of the traps to avoid is the unintentional practice of prescribing additional drugs for the adverse effects of other drugs, the so-called 'prescribing cascade'. For example, the risk of being commenced on antihypertensive treatment is increased in recent users of nonsteroidal anti-inflammatory drugs, gout therapies are more common in users of thiazides, and levodopa is more frequently prescribed to patients taking metoclopramide.[14]

Deprescribing: the medication untrial

There is some evidence for the benefit of reducing medications in subjects with polypharmacy. In a placebo controlled withdrawal trial of psychotropic medications in older subjects taking on average more than five medications, there was a substantial reduction in falls.[15] There have been at least four trials investigating the effect of withdrawal of antihypertensive medications in older people and overall, 40% of subjects remain normotensive.[16] More recently, the Australian National Blood Pressure Study (ANBP2) found that 36% of treated hypertensive older patients who remained normotensive 2 weeks after ceasing antihypertensives, were still normotensive 12 months

Figure 1b. Significant reduction in hip fractures versus women over 80 years of age: no significant reduction in fractures[4]

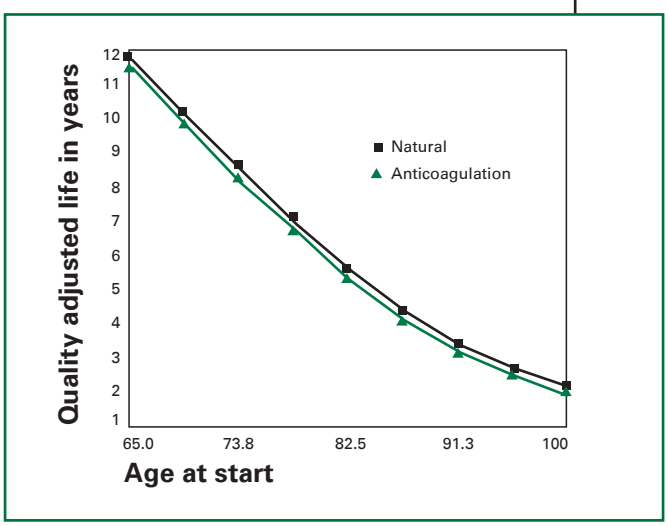

Figure 2. Effects of anticoagulation on quality adjusted life expectancy in older people with atrial fibrillation but no other risk factors for stroke. Anticoagulation had no significant benefit[7]

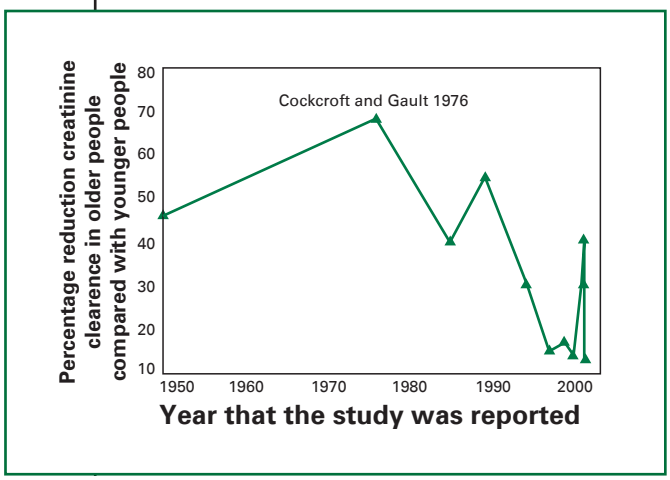

Figure 3. Relationship between the year of study and the percentage reduction in creatinine clearance in older people. The study of Cockcroft and Gault, often used to define doses for renally cleared medications, gives the greatest age related reduction in renal function[1]

later.[17] In a study of drug withdrawal, 238 medications were ceased in 124 subjects. There were no clinical consequences for nearly three-quarters of the medications, and in cases where an adverse withdrawal event occurred, it was mostly angina and heart failure secondary to cessation of beta blockers and diuretics.[18] Likewise, inadvertent cessation of medications on transfer from hospital to nursing home led to adverse events in only 20% of older patients.[19] This study demonstrates a potential role for the GP in monitoring medications during this transition.

Deprescribing is difficult. There are enormous marketing pressures to maintain high levels of prescribing. Prescriber feedback and pharmacist led medication reviews have been tried.[5] General practitioners have also been encouraged to withdraw medications in their older patients with polypharmacy.[5] Most drugs can be stopped without major withdrawal effects. However, abrupt withdrawal of benzodiazepines can be associated with seizures, beta blockers with tachycardia and exacerbation of ischaemic heart disease, and levodopa with neuroleptic malignant syndrome.[5]

Conclusion

The decision to prescribe a medication to an older patient is, like all medical interventions, guided by the ethical principles of:

- Beneficence – 'what is the evidence for the likely benefit in this particular patient?' There is little published evidence for benefit of most pharmacotherapies in frail, older people or in people with comorbidity and multiple medications. Evidence for efficacy is often predicted to be similar to that seen in younger patient groups. Alternatively, GPs can determine whether there is any benefit by trialing the medication in the patient and making a clinical decision as to whether some overall good has been achieved
- Nonmaleficence – 'what are the adverse effects likely to be in this particular patient, given their age, comorbidities and other medications?' Adverse drug reactions are more common in older people and a frequent cause of morbidity and mortality. Polypharmacy exacerbates this problem. The high rate of adverse drug reactions should be balanced against the often uncertain efficacy evidence in older people before a decision to prescribe is embraced
- Autonomy – 'what does the older person want?' Older adults, especially frail older adults, may often be concerned about issues of independence and side effects of medications rather than whether their disease or risk factor is managed according to the latest published guidelines.

Summary of important points

- Analyse clinical trial evidence closely for conclusions relevant to older people.
- Balance evidence for efficacy against the likelihood of adverse drug reactions given your patient's comorbidity, age and other medications.
- Avoid polypharmacy if possible, as it increases the risk of adverse drug reactions and medication errors.
- Allow patients autonomy in the decision to prescribe.
- Choose a dose (usually lower) based on clinical trial data. In the absence of such data, be guided by pharmacokinetic data or generalisations about age related changes in hepatic and renal function.
- Monitor patients closely for efficacy and adverse effects after commencing any new medication.
- Implement deprescribing regimens under supervision in older patients with polypharmacy. Use step down doses where adverse effects may occur (eg. reflex sympathetic stimulation).
- Consider an adverse drug reaction as a possible cause for any clinical presentation in older patients, especially falls and confusion.

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