Sensible prescribing for older people

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The physician treating older people should aim to ensure maximum benefit from medication and as few adverse effects as possible by avoiding excessive, inappropriate or inadequate consumption of medicines. To improve both symptom control and prognosis, a balance must be sought between using the lowest effective dose of the least number of drugs per day for the shortest duration and non-drug alternatives to reduce the incidence of adverse drug reactions (ADRs) (risk and severity of which increase with age,[1,2] polypharmacy and comorbidity[3]) and recommendations for multiple drug interventions.

A broad approach to management of older patients is needed, individualising the evidence about optimal care. Unfortunately, often inappropriately, older people are excluded from clinical trials,[4] so it is difficult to apply research evidence of benefits and risks to this under-represented population. The size of benefit tends to relate to absolute risk; thus, the effect of a particular drug would be expected to be at least as large in older patients as in others but the risk of adverse effects may be higher.

This article will review the effectiveness and appropriateness of drugs in common medical conditions in older people.

Thromboembolic prophylaxis in atrial fibrillation

Randomised trials have confirmed the efficacy of dose-adjusted warfarin therapy (target International Normalised Ratio 2–3) in reducing stroke risk in atrial fibrillation by 68%[5] compared with a 21% risk reduction with aspirin. However, the high rate of intracranial haemorrhage in patients over 75 years taking warfarin almost negates the benefits from ischaemic stroke reduction.[6] For the very old, comorbidities which limit life expectancy also limit potential benefit; the risk-benefit is unclear as only small numbers have been studied. While warfarin can produce similar stroke risk reduction in older people to that observed in trials, there is a higher incidence of bleeding complications. Unstable control of anticoagulation is an independent predictor of bleeding. Factors contributing to instability and falls should be sought and rectified if possible.

Management of myocardial infarction

Thrombolytic agents

Older patients are at higher risk of vascular death after acute myocardial infarction (MI). Although the absolute benefits of thrombolytic treatment are greatest, this age group is more likely to have clinical contraindications.[7] However, it should not be withheld on the basis of age alone.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors reduce morbidity and mortality in patients with ischaemic heart disease and MI.[8] Given early after acute MI, they can show benefit within a day. Absolute benefits are much greater in patients with impaired systolic function, acute cardiac failure or subsequent chronic heart failure, and greatest in more severe heart failure. Long-term reductions in MI, stroke, cardiac arrest and heart failure have been demonstrated from ACE inhibition in patients at high risk of cardiovascular events and without left ventricular dysfunction.[9] ACE inhibitors are contraindicated by:

- pre-existing hypotension: hypotension occurs particularly in patients with heart failure, sodium- or volume depletion,
- renovascular disease:[10] deterioration in renal function occurs mainly in patients with existing renal or renovascular dysfunction or heart failure and may be aggravated by hypovolaemia.

Beta-blockers

Reduced mortality with beta-blockers after acute MI has been reported in studies in patients up to 75 years, with reduced ischaemia and dysrhythmias, and prevention of cardiac rupture. Benefits in the post-infarction period are greatest when left ventricular dysfunction is severe. Beta-blockers (including carvedilol which has vasodilator activity) in chronic heart failure in older people lead to increased ejection fraction and a fall in left ventricular dimensions. They reduce hospitalisation and death, but exercise capacity may not be improved.[11]

Key Points

Prescribers for older people should aim to ensure maximum benefit from medication and minimisation of adverse effects which can result from excessive, inappropriate or inadequate use

Application of research evidence of benefits and risks to older patients is difficult as they are often excluded from clinical trials. Absolute benefit is likely to be at least as large as in younger patients

The risk of adverse effects may be higher for some drugs given to older people and undermine the value of therapy

'Real-life' trials with clinically relevant end-points to improve the evidence base in older people are required

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However, more older patients have relative contraindications (eg postural hypotension).

Aspirin

Meta-analyses of randomised controlled trials (RCTs) of aspirin in secondary prevention of major occlusive vascular events show a reduction of about 25% over a two-year follow-up period. Relative risk reduction is similar in young and older people, but absolute benefit is greater for the high-risk patient over 65 years (4.5% vs 3.2% for under 65s).[12] Aspirin is appropriate for patients with coronary artery disease in the absence of contraindications, which include hypersensitivity, peptic ulceration and haemophilia, as it reduces mortality. There is no overall benefit from primary prevention in low-risk older people as adverse events are more common.

Hypertension

Absolute benefit from antihypertensive medication is much greater for older people than for young people. Evidence supports treatment as a primary prevention strategy at least up to 85 years. The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) of 33,357 participants aged 55 or older with hypertension and at least one other coronary heart disease risk factor showed no difference in fatal ischaemic heart disease or non-fatal MI between chlorthalidone, amlodipine or lisinopril.[13] Chlorthalidone (and, by implication, thiazide diuretics) was more effective in preventing one or more major forms of other cardiovascular disease; as thiazides are less expensive, they are the preferred initial therapy for many patients. Pravastatin significantly reduced neither mortality nor ischaemic heart disease in those (10,356 randomised) with well controlled hypertension and moderate hypercholesterolaemia. Incidence of combined cardiovascular events of fatal and non-fatal coronary heart disease, revascularization surgery, angina pectoris, stroke and congestive cardiac failure, in particular the latter, was 25% greater in patients treated with doxazosin than with chlorthalidone. In contrast, in another trial of 6,083 people with hypertension aged 65–84 years, randomly assigned to hydrochlorothiazide or enalapril and followed for a median of 4.1 years, there were 56.1 and 59.8 cardiovascular events or deaths per 1,000 patient-years in the ACE and diuretic groups, respectively.[14]

These studies are not directly comparable. The seemingly conflicting results indicate that evidence can provide guidance on treatment but not standardisation. Doctors must be guided by individual patients' response to therapy.

There are fewer MIs and episodes of heart failure in older patients on ACE inhibitors than with calcium-channel blockers, and also in diabetic patients in whom they slow progression of renal disease.[15] A strategy gaining in popularity is to use an ACE inhibitor or beta-blocker as first-line, with a calcium-channel blocker or diuretic as add-on for young patients who are likely to have raised renin (the opposite approach is taken in older or African-Caribbean people whose renin is likely to be low).

Other concepts also increasingly used include, for example, nitric oxide donors in older subjects with wide pulse pressure (and by implication, a 'stiff' arterial system).

Hyperlipidaemia

The Heart Protection Study assessed the effect of simvastatin 40 mg in 20,536 adults aged 40–80 years with coronary disease, other occlusive arterial disease or diabetes mellitus. Statins were shown to be of benefit, irrespective of age or initial cholesterol level.[16] There was no statistically significant reduction of major vascular events in the first year, but in each year thereafter there was a significant reduction of about 25% ($p < 0.0001$) in first event rate of MI, stroke and revascularisation; this was proportionally similar in those aged under or over 70 years at entry. Benefit depends on an individual's overall risk rather than lipid concentration. Where a patient's quality of life is positive and life expectancy exceeds one year, statin therapy should be considered for the patient with occlusive arterial disease or diabetes, irrespective of age, given the evidence for prognostic benefit.

Centrally acting drugs

Antidepressants

The National Service Framework on Mental Health recommends that tricyclic antidepressants should not be prescribed for patients over 70 because of the increased likelihood of adverse effects. Published clinical evidence supports the use of selective serotonin reuptake inhibitors as first-choice agents for treating late-life depression.[17] There are few data and no clear evidence about difference in efficacy of antidepressants but unwanted effects differ. Marked differences in their effects on specific cytochrome P450 isoenzymes influence their potential for pharmacokinetic interactions at this level. When choosing an antidepressant consider previous treatment response, its efficacy, safety and pharmacokinetic issues as well as comorbid conditions and comparative costs.

Antipsychotics

For dementia patients with disruptive behaviour, non-drug interventions to orientate and calm should be tried. There is little evidence from RCTs to support the use of antipsychotic drugs,[18] no study having shown a difference between response to conventional antipsychotics or placebo, although meta-analyses have shown improvement in some behavioural symptoms. Tardive dyskinesia and anticholinergic effects can be difficult and conventional neuroleptics may hasten cognitive decline. Atypical antipsychotics (eg risperidone and olanzapine) can reduce psychosis, agitation and aggression, but there may be somnolence, oedema and extrapyramidal effects. Carbamazepine can reduce agitation and aggression at the expense of ataxia and drowsiness, but valproate appears to have no effect.

It is important to treat intercurrent ill-

ness and address aggravating physical and environmental factors before using antipsychotic drugs as a last resort in patients with severe behavioural disturbance. Treatment should be started with a low dose, increasing it slowly, with reduction or withdrawal if there are adverse effects or no beneficial effect.

Benzodiazepines

Older patients are particularly susceptible to falls and central nervous system depression on benzodiazepines. Most prescriptions for benzodiazepines are for insomnia, anxiety or many non-specific symptoms for which the evidence of benefit is poor. The risk of ADRs increases with age, so attempts should be made to wean older long-term users from these drugs.

Osteoporosis

Treatment

Calcium supplements. Bone loss is decreased by calcium supplements, but not to the same extent as by antiresorptive agents. They should be co-administered with vitamin D or biphosphonates (cyclical or regular) as there is no convincing evidence that they lower risk of vertebral or hip fracture when given alone. For frail older people, those at increased risk of falls and the housebound whose exposure to sunlight is low, a dose of 800 iu of vitamin D daily, preferably with 0.5–1 g calcium reduces the risk of hip fractures.[19] A risk assessment for falls and advice and consideration of hip protectors are recommended. The reduced incidence of fractures (such as Colles' fractures) noted with calcium and vitamin D is due to a moderate increase in bone density and other beneficial systemic effects.

Fragility fractures. Fragility fractures are those occurring on minimal trauma after the age of 40 and include forearm, spine, hip, ribs and pelvic fractures. In the presence of one or more documented fragility fractures, biphosphonates, calcitonin, calcitriol, hormone replacement therapy (HRT) and raloxifene are recommended, with vitamin D and calcium as adjuncts to treatment.

There is little information on the relative efficacy of biphosphonates in the management of osteoporosis in patients over the age of 80 years. Calcitonin can be useful for pain relief in acute fracture and in osteoporosis not sufficiently responsive to biphosphonates. Secondary prevention trials of management of osteoporosis after hip fracture are ongoing. Although HRT is available for the prevention and treatment of osteoporosis, it is poorly tolerated when introduced in old age and increases risk of stroke, venous thromboembolism, breast and ovarian cancer.

Corticosteroid related osteoporosis. Oral glucocorticoids are associated with an increase in fracture risk at the hip and spine, the greater increase in relative risk being observed with higher dose therapy. Calcium and vitamin D can have an important role in prevention of corticosteroid related osteoporosis, but biphosphonates are the first option for treatment. There are evidence-based guidelines for the management of glucocorticoid-induced osteoporosis.[20]

Conclusion

Older people are not adequately included in clinical trials, which makes applying RCT evidence to them difficult. There is a gap between evidence required to secure a licence for a new drug and evidence needed to make a clinical judgement about its role, particularly in older people. Real-life trials with clinically relevant end-points to improve the evidence base in this group are required.

In the meantime, we must make do with what knowledge is available. In general, the benefit patients receive from any one drug is not influenced by any other drug therapy. Where life expectancy allows, drugs which improve well-being and prognosis should be introduced.

In heart failure, however, there is evidence that addition of a third agent to the other two, be it an ACE inhibitor, angiotensin-II receptor antagonist or beta-blocker, increases the risk of adverse effects and so limits prescribing. In any situation, the risks of an adverse effect are influenced by comorbidity and other medicines which may provide an absolute or relative contraindication.

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Delirium

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Delirium (acute confusional state) is a common and unpleasant condition in older people that can have serious short- and long-term consequences. It is often misdiagnosed or unrecognised by doctors and nurses, and management is often poor.[1]

Clinical features and diagnosis

A diagnosis of delirium should be considered when a patient is described as, or thought to be, 'confused', 'vague', 'a poor historian' or 'unco-operative'.

Delirium is characterised by a change of cognition that develops over hours or days (Table 1). Symptoms fluctuate throughout the day and are worst at night. Disturbed consciousness and inability to attend to the environment are cardinal features: patients are highly distractable and find it difficult to focus or sustain concentration. They are often disoriented with rambling, incoherent speech and may be tearful or anxious. Persecutory delusions and visual hallucinations are common.

Table 1. Diagnostic criteria for delirium.

- Disturbance of consciousness (reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention
- A change in cognition (such as memory deficit, disorientation, language disturbance or perceptual disturbance) not better explained by a pre-existing or evolving dementia
- The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate over the course of the day
- There is often evidence from the history, physical examination or laboratory findings that the disturbance is due to one or more medications or general medical conditions

Two distinct clinical subtypes of delirium are recognised:

- an *agitated variant* with psychomotor overactivity, such as plucking at bedclothes or aggression, and
- a *quiet variant* where patients appear apathetic and withdrawn; this is easily missed or misdiagnosed as depression.

A history from a carer of the onset of the cognitive disturbance is invaluable in distinguishing between dementia and delirium. Delirious patients can often be recognised at the bedside from their characteristic distractability. Impaired attentiveness can be assessed formally with bedside tests such as asking the patient to say the months of the year backwards or to count backwards from 20.

Generalised slowing of the EEG trace is characteristic of delirium (withdrawal states excepted), but the specificity of this finding is reduced with increasing age and in dementia.

The prevalence and incidence of delirium are shown in Table 2.

Outcome

Delirium is traditionally regarded as a transient disorder, but 30–60% of delirious patients still have clinically significant new cognitive impairment several weeks later, and subsequently there is an increased risk of developing dementia.[4] It remains uncertain whether delirium is simply a marker for reduced cognitive reserve or whether it may of itself cause structural brain damage.

In reports from widely diverse healthcare systems, even after adjusting for potential confounding factors, delirium has consistently been associated with:[5]

- prolonged hospital stay
- functional decline, and
- increased risk of institutionalisation.

Complications such as pressure sores, falls, infections and urinary incontinence