
GERIATRIC THERAPEUTICS

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Health Promoting Medications in Older People

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ABSTRACT

As we approach the new millennium, greater emphasis will need to be placed on preventive strategies that improve the quality of life in people who survive to old age. This review focuses on medications that may be beneficial in the primary prevention of a number of common conditions that affect older people, where evidence already exists of significant benefit. These common diseases include infectious diseases, cardiovascular and cerebrovascular disease, and osteoporosis. **Aust J Hosp Pharm 1999; 29: 273-8.**

VACCINATION

Influenza

Although some studies have suggested that the induction of serum antibody to influenza with vaccination in older people was reduced compared with younger persons, clinical studies have shown effective protection. A large study (>25 000) in the US over consecutive influenza seasons showed a large reduction in pneumonia and influenza hospitalisation (51.2%), reduction in respiratory condition hospitalisations (32.5%), cardiac failure hospitalisations (28.6%), and outpatient visits (17% pneumonia and influenza visits) and reduction of costs (30.7% for all respiratory cardiac failure admissions).¹ A recently published study has demonstrated the efficacy of yearly influenza vaccination in the older person.²

The current recommendation of the Australian Society for Geriatric Medicine is for all people aged 65 and over to be vaccinated annually and also for all persons in long-term care and residential facilities.³

There are very few adverse effects with the advent of more purified vaccines available over the past few years. Local reactions occur at a rate of 15-20%, and non-specific systemic symptoms occur at a rate of less than 1%. Anaphylactic reactions are extremely rare. Those persons allergic to egg should not be vaccinated,

because of the theoretical risk of anaphylaxis.

One of the main issues is compliance with immunisation. In one survey in the US, only 34% of over 65-year-olds surveyed had had influenza vaccination. The vaccine was significantly accepted by patients who had been advised by their doctor to be vaccinated yearly. These patients had a vaccination rate of 96.4%, emphasising the need for education.⁴ The rate of influenza vaccination in Australia was 165/1000 of the population in 1998. In a study of free vaccination for over 65-year-olds in Victoria, approximately 70% received the vaccine (personal communication with Alan Hampson, Deputy Director, WHO Reference Centre). Fortunately the influenza vaccine was available free to all Australians aged 65 years and over in 1999.

Pneumococcal Vaccination

Pneumonia is more common in older people and the associated mortality is high. Pneumococcal pneumonia is a common cause of bacterial pneumonia. Whether older persons mount an adequate antibody response to pneumococcal vaccination is debatable.^{5,6} A recent trial in Sweden found that in 691 non-immunocompromised people aged 50-85 years who were randomised to either placebo or 23-valent pneumococcal vaccine, there was no difference in death rate nor in risk of developing pneumococcal pneumonia.⁷ However, in another larger study including 2837 subjects, vaccination was effective in preventing pneumonia in 59% of people aged 60 years and older.⁸

In a study spanning 14 years (1978-92), the incidence of pneumococcal pneumonia in immunocompetent people older than 65 years decreased by 75% with pneumococcal vaccination.⁹

The current recommendation by the National Health and Medical Research Council in Australia is to vaccinate all people over age 65 years who have co-existing medical illness such as cardiorespiratory disease, diabetes, asplenia or malignancy. The Australian Society for Geriatric Medicine recommends that strong consideration should be given to vaccinating all people over 65, even without coexisting disease.³

Local reactions to the vaccine are very common (30-50%), systemic reactions are uncommon (<1%) and

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severe systemic reactions rare. Revaccination should be considered after six years.³

Tetanus

Although tetanus vaccination has been available since the 1940s, many people, particularly older persons, do not have immunity to tetanus. A recent survey in the US showed that in those aged 70 years or older, only 27.8% had effective levels of tetanus antibodies.¹⁰ Tetanus is an effective vaccination with vaccination rates correlating well with antibody levels; however, immunity wanes with time. Older persons are at risk of contracting tetanus. Their immunisation history is often unreliable.¹¹ Current recommendations are to vaccinate those without a primary course and give 10-yearly boosters with tetanus toxoid.³ In developed countries a substantial number of the people who contract tetanus are older adults.¹²

LIPID LOWERING THERAPY

There is a well established link between elevated serum cholesterol and the development of ischaemic heart disease and mortality from cardiovascular disease.¹³ This link also extends to older people,¹⁴ although the association between elevated cholesterol and the risk of cardiovascular events decreases with age. However, because of the increased risk of cardiovascular disease with age, the attributable risk for elevated cholesterol increases with age, suggesting that there may be substantial benefits from the treatment of older people with lipid lowering therapy.¹⁵ Most research examining the effects of cholesterol reduction has involved the middle-aged population with little research specifically looking at the older person, let alone the very old (80 plus).

Cholesterol Reduction in Coronary Artery Disease

Early trials of cholesterol lowering used agents such as clofibrate, colestipol, cholestyramine and gemfibrozil in primary prevention.¹⁶⁻¹⁹ Whilst these trials demonstrated a significant reduction in cardiovascular disease and cardiovascular mortality, they did not show a reduction in total mortality. Secondary prevention studies before the availability of HMG-CoA reductase inhibitors also showed a reduction in cholesterol and in cardiovascular events.²⁰⁻²²

Clinical trials using HMG-CoA reductase inhibitors (statin therapy) have been shown to be of benefit both in primary and secondary prevention of cardiovascular disease. They are beneficial in reducing total mortality, cardiovascular events, hospitalisations, and requirement for revascularisation.

The first major trial to demonstrate a significant decrease in all-cause mortality was the Scandinavian Simvastatin Survival Study, or 4S.²³ This was a secondary prevention trial in 4444 patients with documented coronary artery disease who were followed for an average of 5.4 years. The relative risk of death in the simvastatin group was 0.70 (95% CI 0.58-0.85), relative risk of a coronary death 0.58 (95% CI 0.46-0.73), and relative

risk of a major coronary death 0.66 (95% CI 0.59-0.75). Importantly, benefits of cholesterol lowering occurred early. There was a very significant reduction in revascularisation procedures (RR 0.63, 95% CI 0.54-0.74), and also a decrease in days spent in hospital.

When a cohort of 65-70-year-olds within the 4S trial were examined, it was found that cholesterol lowering was similar to the entire study cohort.²⁴ There were similar reductions in relative risk for coronary events in the older cohort. However, because mortality rates substantially increase with age, the absolute risk reduction for both all-cause mortality and coronary artery disease mortality was substantially greater in the older patients.

Another major trial to show benefit to the older person was the CARE (Cholesterol and Recurrent Events) study.²⁵ This study demonstrated that lipid lowering, in secondary prevention, with patients who had what was considered a 'normal' cholesterol significantly reduced coronary events and coronary mortality.

The role of primary prevention in patients with hypercholesterolaemia using statin therapy has been examined in the WOSCOPS (West Of Scotland) Trial.²⁶ This involved 6595 men, aged between 45 to 65 years (mean age 55 years), with raised cholesterol who were considered high risk. There was a significant reduction in total and LDL cholesterol, fatal and non-fatal coronary events, as well as total mortality. Again benefit occurred early, within six months of treatment.

Cholesterol Reduction in Cerebrovascular Disease

The relationship between serum cholesterol levels and risk of stroke is now becoming more clear cut. In the 4S and CARE studies fewer cerebrovascular events occurred. A recent meta-analysis showed that there were significant decreases in stroke both in primary and secondary prevention trials using statin therapy.²⁷ In this meta-analysis, a total of 29 000 patients were examined with a mean follow-up for 3.3 years. There was an average decrease in total and LDL cholesterol of 22% and 30% respectively in patients receiving statin therapy. There was a 29% risk reduction of stroke (95% CI 14%-41%), which was significant, as well as total reduction in mortality of 22% (95% CI 12%-31%).

This meta-analysis again confirms that there is no evidence of increased non-cardiovascular mortality with the use of statins and the lowering of cholesterol, and no increase in the risk of cancer. The older population was not specifically isolated as a subgroup in this meta-analysis, but as discussed above, treatment of hypercholesterolaemia is likely to offer greater benefits compared with younger age groups.

The evidence concerning the benefit of treatment of isolated elevated triglyceride levels is unclear at this stage.²⁸

DRUG TREATMENT OF HYPERTENSION

It is well established that treatment of hypertension in the older person results in a significant reduction of

total mortality and cardiovascular morbidity and mortality. This has been shown in several meta-analyses of patients aged 60 years and older.^{29,30} The benefit of treating the very old and frail may be diminished. This may be because those very old people with hypertension are survivors and those who are susceptible to the injurious effects of prolonged hypertension have already died. However the SHEP trial found no less benefit in the very old.³¹ The SHEP study showed that a reduction of 11 mmHg systolic blood pressure in the treatment group resulted in a 36% decrease in the risk of stroke (RR 0.64, 95% CI 0.50-0.82). Therefore active treatment of hypertension should be undertaken regardless of age, especially with the availability of newer, better tolerated agents.

Hypertension is the most significant risk factor associated with stroke,³² including in the older person. This includes both diastolic and systolic hypertension, which are both associated with ischaemic and haemorrhagic stroke.³³

Reduction of stroke in the older person is an important aim as it is one of the major causes of morbidity and mortality. In one meta-analysis, there was an odds ratio of 0.64 (95% CI 0.49-0.82) in stroke mortality and 0.65 (95% CI 0.55-0.76) in stroke morbidity with treatment of hypertension.³⁴ This same analysis showed an odds ratio reduction of coronary mortality and morbidity of 0.75 (95% CI 0.64-0.88) and 0.85 (95% CI 0.73-0.99) respectively.

ASPIRIN IN PRIMARY PREVENTION IN OLDER PEOPLE

Aspirin Use in Vascular Disease

Although there have been two clinical trials which examined the role of aspirin in primary prevention of stroke, it remains unclear whether aspirin is beneficial. Both trials used relatively high doses of aspirin, 325 mg every second day in the Physicians' Health Study³⁵ and 500 mg daily in the British Male Doctors' Trial.³⁶ There was an increased risk of haemorrhagic stroke, which was significant, in the Physicians' Health Study. There was no significant difference in the incidence of stroke between those taking aspirin and controls in the British Doctors' Trial.

The Physicians' Health Study did show a 44% reduction (RR 0.56, 95% CI 0.45-0.70) in fatal and non-fatal myocardial infarctions; however, there was no reduction in stroke and total cardiovascular deaths in those taking aspirin. There was no reduction in myocardial infarctions in those taking aspirin in the British Doctors' Trial.

The Antiplatelet Trialists' Collaboration used the technique of meta-analysis to examine the use of aspirin in low risk patients and found that reductions in vascular events were small and not statistically significant.³⁷ There was however, a small reduction in non-fatal myocardial infarctions (2.0% in controls vs 1.5% in antiplatelet groups). This was offset by a significant increase in non-fatal strokes (1.0% in controls vs 1.2%

in antiplatelet groups).

There is no evidence that currently supports the use of aspirin in primary prevention of cardiovascular or cerebrovascular disease. The use of aspirin in secondary prevention of coronary artery disease and stroke is well established.

Aspirin in Prevention of Colorectal Cancer

The majority of studies evaluating the use of aspirin in possible prevention of colorectal cancer are observational. Most of these have demonstrated a protective effect with the use of NSAIDs (mainly aspirin) against colorectal cancer occurrence and mortality.³⁸⁻⁴¹ Secondary analysis of the Physicians' Health Study, as discussed above, did not show a benefit in preventing colorectal cancers on an aspirin dose of 325 mg every second day.⁴²

A randomised controlled trial, designed to address this question is required and one is currently underway.⁴³ This trial is examining the incidence of polyp recurrence in patients with a history of polypectomy, who will be given either placebo or aspirin. At present there is insufficient evidence to recommend the regular use of aspirin for primary prophylaxis of colorectal cancer.

HORMONE REPLACEMENT THERAPY

Oestrogen therapy is effective in preventing postmenopausal bone loss.⁴⁴ A meta-analysis, based on observational data, has observed that there is a 25% (pooled RR 0.75, 95% CI 0.68-0.84) reduction in the risk of hip fracture in current users of oestrogen.⁴⁵ There have been no randomised controlled trials of the effect of hormone replacement therapy on hip fractures.

A prospective cohort study of 9704 women aged 65 years or over found that current oestrogen use decreased the risk of fracture.⁴⁶ There was a decrease in risk for wrist fractures (RR 0.39, 95% CI 0.24-0.64), all non-spinal fractures (RR 0.66, 95% CI 0.54-0.80) and hip fractures (RR 0.60, 95% CI 0.36-1.02) in those using oestrogen, whether it be combined with a progestin or alone, regardless of whether they were smokers or non-smokers, and independent of whether they were over or under 75 years of age. This study showed more benefit to those who started their oestrogen therapy within 5 years of menopause with a RR for wrist fracture of 0.29 (95% CI 0.13-0.68), for non-spinal fracture 0.50 (95% CI 0.36-0.70), and 0.29 for hip fractures (95% CI 0.09-0.92).

The Postmenopausal Estrogen/Progestin Intervention (PEPI) trial involved 875 postmenopausal women randomised to either oestrogen alone or combined with a progestin, or placebo.⁴⁷ Results showed a reduction of 10-12% in LDL and an increase of 4-8% in HDL in those taking oestrogen either alone or in combination, suggestive that oestrogen therapy may be beneficial in prevention of cardiovascular disease. In the PEPI trial there was an associated increase in triglycerides of 15-20%. One meta-analysis, of mainly observational data, found oestrogen use is associated with a decrease in

risk of coronary artery disease of 35% (pooled RR 0.65, 95% CI 0.59-0.71).⁴⁵

Patients taking hormone replacement therapy for 15 or more years have been found to have a significantly lower mortality (RR 0.54 of all-cause mortality), as published recently in 232 users of HRT compared with non-users.⁴⁸ However, a recent randomised study has not confirmed the benefits for secondary prevention of cardiovascular disease.⁴⁹ There was no significant difference between placebo or treatment groups over four years and therefore HRT cannot as yet be recommended solely for this purpose.

Oestrogen therapy reduces the symptoms of menopause, including urogenital symptoms.

The safety of long-term hormone replacement therapy has been called into question. It is well known that unopposed oestrogen increases the risk of endometrial cancer. This risk is increased with higher doses and prolonged therapy, in fact the RR is 9.5 (95% CI 7.4-12.3) after 10 or more years of treatment with unopposed oestrogen.⁵⁰ However, when combined with a progestin the RR is 0.8 (95% CI 0.6-1.2).

There is no definitive evidence in relation to hormone replacement and risk of breast cancer. At present a meta-analysis has shown no clear evidence with short-term oestrogen exposure. There is only a possible risk with long-term oestrogen use, either alone or in combination with a progestin (pooled RR 1.25, 95% CI 1.04-1.51).⁴⁵ There is little data available on thrombotic risk in women taking hormone replacement.

There are problems with long-term compliance with hormone replacement therapy. A recent survey of 7667 women aged 65 years and over found that only 17% were taking hormone replacement and 27% discontinued treatment because of perceived lack of benefit. In the group of women not taking oestrogens, 38% thought that hormone replacement was harmful.⁵¹

In summary, hormone replacement may have multiple benefits, especially with regard to the potential reduction in cardiovascular disease, which remains the main cause of mortality and morbidity in the older woman, with additional reduction in the risk of osteoporotic fractures, but with the possible deleterious effect of breast cancer. Other issues with the long-term use of HRT include compliance and the 'medicalisation' of normal women. A large randomised trial is required and is currently underway in North America, the Women's Health Initiative.

The selective oestrogen receptor modulator raloxifene has recently been shown to decrease the risk of E2-receptor positive breast cancer among postmenopausal women followed for three years.⁵² Raloxifene has also been shown to decrease the risk of vertebral fractures in postmenopausal women with osteoporosis and increase bone density, but with an increased risk of venous thrombosis.⁵³

CALCIUM AND VITAMIN D

The combination of calcium plus vitamin D has been

shown to be useful in reducing non-vertebral fractures in both ambulatory nursing home residents and in older persons living at home. In a study involving 3270 women with average age 84 years, subjects were given either 1.2 g of calcium per day plus 800 IU per day of vitamin D₃ or double placebo for 18 months. Those given calcium plus vitamin D₃ had a reduced risk of hip fracture by 43%, increased bone mineral density as measured by DEXA at the proximal femur and a reduction of other non-vertebral fractures by 32%.⁵⁴ A further study of both men (176) and women (213) living in the community aged 65 years or older, found that three years of dietary supplementation of calcium plus vitamin D₃ reduced bone loss and the incidence of non-vertebral fractures.⁵⁵

Vitamin D alone has not yet been shown to be of benefit in reducing fractures; however, all older persons should be treated for deficiency. One study did not find any benefit in reducing bone loss with vitamin D supplementation.⁵⁶ Vitamin D compared with placebo over a three-year period was not shown to be effective in preventing hip fractures.⁵⁷ Vitamin D versus placebo was also not shown to be of benefit in preventing other appendicular skeletal fractures.⁵⁸

There is some benefit afforded by calcium supplementation as it appears to slow the rate of bone loss.⁵⁹ One randomised controlled study has confirmed the sustained benefit of calcium supplementation in postmenopausal women in reducing rate of bone loss over four years.⁶⁰ The difference in fracture rate between the groups was significant, although the study size was too small for this to be regarded as a definitive study. A further study assessing vertebral spine fracture rate over about four years in elderly women randomised to either calcium supplements or placebo, found those receiving calcium who had recently had a vertebral fracture were significantly less likely to have another in the follow-up period.⁶¹ Adequate dietary intake of calcium should be recommended for all postmenopausal women, and supplementation for those whose diet is inadequate.

CONCLUSION

The medical conditions reviewed here have evidence that certain medications may benefit the older person and improve their quality of life. Most research has focused on younger age groups, but good evidence exists that the older person will benefit from primary and secondary prevention strategies with the use of certain medications. This should be coupled with lifestyle modifications such as a healthy diet and regular exercise.

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