Learning objectives:
After reading this article, the reader should be able to:

- Describe some of the nutritional challenges in the elderly;
- Summarise the current evidence surrounding the use of B-group vitamins, calcium and vitamin D; and
- Discuss how this evidence will influence your practice.

Introduction
It has been estimated that Australians spend approximately $4 billion annually on complementary and alternative medicine (CAM; includes purchases of products and visits to practitioners), just under half of which is spent on CAM products. Spending on CAM products equates to roughly half of all non-subsidised health care products in Australia. While the elderly appear less likely to use CAM products and visit CAM practitioners than their younger counterparts, 58% and 35% of Australians over 65 years of age admitted to using a CAM product or visiting a CAM practitioner within the past 12 months, respectively, in a recent nationwide survey. The most frequently used CAM product type in Australian representative surveys is clinical nutrition, accounting for 40–50% of CAM product usage. In this article we will review recent evidence relating to the use of vitamin supplements in the elderly, particularly B-group vitamins, calcium and vitamin D.

Nutrition in the elderly
The elderly present several nutritional challenges: they are the largest group of nutritionally vulnerable people in Australia (with those in residential aged care at greatest risk); there is a simultaneous reduction in energy requirements and increasing requirements for a number of nutrients (e.g. protein, riboflavin, pyridoxine, calcium, vitamin D and vitamin B12) with advancing age, and these issues are compounded by a reduction in appetite. It may therefore be difficult for the elderly to meet minimum nutritional requirements from their diets alone, and fortified foods and/or vitamin supplements may be required. The recently published Nutrient Reference Values (NRVs) for Australia and New Zealand now present differing recommended nutrient intakes for various age groups.

Suboptimal nutrition
Suboptimal nutrition is defined as a state in which nutritional intake is sufficient to prevent the classical symptoms and signs of deficiency, yet insufficient to significantly reduce the risk of developmental or degenerative diseases. In some cases, high-level scientific evidence exists to support supplementation to reduce the rate of clinical events. For example, the use of folate supplementation in pregnancy to prevent neural tube defects, and calcium and vitamin D supplementation in elderly women with osteoporosis. There has also been strong awareness that nutritional intakes beyond the recommended daily intake may have a role in the prevention of some chronic diseases which are often associated with advanced age, such as cardiovascular disease, stroke, macular degeneration, dementia and cancer.
B-group vitamins

In the 1960s it was proposed that homocysteine was a cause of arterial and venous thrombotic disease. This theory was based on the observation that children with extremely elevated homocysteine levels due to inborn metabolic errors suffered from premature atherothrombotic disease. Similarly, it was observed that patients with Alzheimer’s disease had higher plasma levels of homocysteine (regardless of the presence of cerebrovascular disease) than age-matched controls. An inverse relationship has been demonstrated between B-group vitamins (e.g. folic acid and vitamin B12) and plasma homocysteine levels. Elevated homocysteine levels have been linked directly to an increased risk of cardiovascular disease, stroke and dementia in observational studies. Homocysteine is a sulfur-containing amino acid derived from methionine, and in experimental settings promotes oxidative stress, endothelial damage and dysfunction, inflammation, thrombosis and cell proliferation. Folic acid and vitamin B12 are required for the methylation of the homocysteine molecule. In combination with vitamin B6 they effectively lower serum homocysteine levels through regeneration of methionine.

a. Cardiovascular disease

While plasma homocysteine levels can be easily reduced by supplementation with B-group vitamins (vitamin B6, vitamin B12 and folic acid), randomised controlled trials (RCTs) do not provide clear evidence that B-group vitamins are beneficial in cardiovascular disease risk reduction. A large number of RCTs conducted in North America and Europe, mostly in patients with pre-existing vascular disease, have failed to show a benefit of B-group vitamins on cardiovascular risk. In fact, in two studies where folic acid was given in combination with other B-group vitamins (vitamin B6 and vitamin B12), in high doses, there was a suggestion that the combination actually increased cardiovascular risk. The vitamin dosages in these studies were 0.8–2.5mg folic acid, 40–50mg vitamin B12 and 0.4–1mg vitamin B6. The comparable RDIs for these vitamins are 0.4mg, 1.3–1.7mg and 0.002mg, respectively for adults. Finally, a 2006 meta-analysis of RCTs confirmed that folic acid supplementation did not reduce the risk of cardiovascular disease or mortality in patients with pre-existing vascular or renal disease. Based on this evidence, B-group vitamins cannot currently be recommended for the prevention of cardiovascular disease.

b. Stroke

While the HOPE-2 study did not show a reduction in its primary outcome (a composite of death from cardiovascular disease, myocardial infarction and stroke), it did find a reduction in the risk of stroke (a secondary outcome). This result was not found in another RCT designed specifically to investigate the effects of homocysteine lowering in patients with a history of stroke. A recent meta-analysis, however, found that folic acid supplementation (at a dosage of 0.8–15mg/day) did reduce the risk of stroke, although the finding was of borderline statistical significance. A greater beneficial effect from folate supplementation was seen in trials of longer duration (>36 months), in those with a greater decrease in plasma homocysteine, in patients who lived in countries with no mandatory grain fortification (which, as you would expect, tends to nullify the benefit of supplementation) and in patients with no prior history of stroke. It is also important to recognise that the patients without a history of stroke in this analysis had significant baseline cardiovascular disease (34% to 55% had significant cardiovascular disease). Based on this information, it is difficult to justify the use of folate supplementation; B-group vitamin supplementation does not appear to be beneficial in patients who have a history of stroke (although this may be because trials need to be longer in duration) and B-group vitamin supplementation may further increase the risk of cardiovascular disease in those at risk of both cardiovascular disease and stroke. Based on the current evidence, we can not be certain that the benefits of B-group vitamin supplementation at the doses studied to reduce the risk of stroke outweigh the risk of other adverse cardiovascular outcomes, particularly in countries (such as the USA and Australia) where food sources are fortified with folate.

c. Dementia

The combination of elevated homocysteine levels and low levels of vitamin B6, vitamin B12 and folic acid has been associated with decreased performance on cognitive tests, and may contribute to the pathophysiology of Alzheimer’s disease by contributing to the formation of amyloid plaques (microvascular disease) and neurofibrillary tangles (oxidative stress). A meta-analysis of 14 small RCTs in 2007 concluded that the evidence did not support the use of vitamin B6, vitamin B12 or folic acid alone, or in combination, on cognitive function testing in people with either normal or impaired cognitive function. The meta-analysis was limited by the inclusion of few studies of significant enough size or duration to assess a change in cognitive function. The FACIT RCT enrolled people whose folate status was suboptimal; participants had elevated plasma homocysteine in the absence of disorders or diseases that could account for the raised level (e.g. vitamin B12 deficiency or renal disease), and were otherwise healthy. In this population, the supplementation of 0.8mg folic acid per day for three years led to expected significant increases in folate status and a reduction in plasma homocysteine. These changes were accompanied by significant improvements in memory, information processing speed and sensorimotor speed. Other trials assessing the effect of B-group vitamin supplementation on cognitive function have failed to provide any evidence of benefit. The most recent RCT in this area investigated the effects of high-dose B-group vitamin supplementation in North American patients with mild to moderate Alzheimer’s disease. In this...
study, patients received 5mg folate, 25mg vitamin B₆ and 1mg of vitamin B₁₂ per day. Despite resulting in a significant reduction in homocysteine levels, vitamin B supplementation failed to result in significant changes in cognitive function. A chance finding was that significantly more patients receiving B-group vitamins suffered from depression, despite no difference in the use of antidepressants between the groups. These results support the conclusion that B-group vitamins are not effective in slowing cognitive decline in individuals with normal folate and vitamin B₁₂ levels in societies with folate-enriched foods.

**Calcium and vitamin D**

Calcium and vitamin D have been shown to reduce the risk of fracture in institutionalised elderly women who are deficient in calcium and vitamin D. Similarly, none of the anti-resorptive therapies (e.g. bisphosphonates and strontium) have been shown to be effective without co-administration of calcium and vitamin D. The role of calcium and vitamin D preventive therapy for fracture in women living in the community is less clear. In a sub-study of the Women's Health Initiative, 36,282 healthy women aged between 50 and 79 years were randomised to receive either 1000mg elemental calcium with 400 IU of vitamin D₃ or placebo. Over a follow-up period of seven years, the rate of hip fractures did not differ significantly between the two groups, although hip bone density improved in the group receiving calcium and vitamin D. However, in women adherent to calcium and vitamin D (defined as taking >80% of study medication doses) the risk of hip fracture was significantly reduced compared to those taking placebo. Other than a slightly increased risk of renal stone formation, no significant risks or additional benefits were associated with calcium and vitamin D supplementation. A RCT in a group of Western Australian women aged over 70 years who received either 1200mg of calcium per day or placebo for five years also found that in the overall study population, calcium supplementation did not significantly reduce fracture risk. However, when women who were adherent (>80% of study medication doses) to calcium supplementation were considered (~60% of the overall study population), calcium supplementation was effective in reducing fracture rates. Finally, a recent meta-analysis confirmed that calcium alone and in combination with vitamin D successfully reduced the risk of fractures of all types in women over the age of 50 years. Fracture risk reduction was greater in women who received calcium and vitamin D supplements, were adherent to therapy, were institutionalised, had a low dietary intake of calcium (<700 mg/day), received supplemental calcium doses of >1200 mg per day and supplemental vitamin D doses >800 IU per day. The degree of fracture risk reduction also increased with age. It is clear that good adherence to calcium is critical in achieving a fracture risk reduction - no significant benefit from calcium supplementation was seen in non-adherent patients (<80% of doses taken).

In spite of the beneficial effect of regular calcium supplementation in elderly women, the safety of calcium supplementation was recently called into question by the results of a RCT from New Zealand. This study involved 1,471 postmenopausal women (mean age 74 years) who were randomised to receive 1000mg calcium or placebo for five years. These women did not receive vitamin D, but women with low vitamin D status were excluded from the trial. In this study, women who received calcium were twice as likely to suffer a myocardial infarction than their counterparts. The results of this study suggest that in elderly women without a previous osteoporotic fracture, the risk of myocardial infarction might outweigh the benefits of calcium supplementation. The Women's Health Initiative study did not show evidence of an increased risk of myocardial infarction, but the younger age of participants and poor adherence to study medications in that study may have contributed to this result. Until this concern has been addressed with additional data and further analysis of additional trials, the safety of calcium supplementation alone in elderly women is under question.

The reduction in fracture risk associated with vitamin D is often attributed to its effect on bone mineral density, but it may also directly increase muscle strength, thereby reducing fracture risk by preventing falls. A systematic review concluded in 2004 that vitamin D reduced the risk of falls in both the institutionalised and ambulatory elderly. This review was limited in that it included studies using various metabolites of vitamin D, which are not necessarily as safe for dietary supplementation as ergocalciferol (D₂) or cholecalciferol (D₃). Another review was less positive, and suggested the lack of effectiveness might be due to variations in the calcium status of patients. A recent RCT recruited 302...
community-dwelling elderly Western Australian women aged between 70 and 90 years and randomised them to receive either vitamin D (ergocalciferol 1000U/day) and calcium supplementation (1000mg/day) or calcium supplementation alone. These women had a history of falling in the previous year and low vitamin D status. Vitamin D reduced the risk of falling at least one fall over one year. The risk of falling was reduced mostly in winter and spring, but not in summer or autumn. Other studies have found that the risk of fractures is higher in the colder months when vitamin D levels are lower due to a lower skin exposure to the sun. Vitamin D (cholecalciferol) is more potent than ergocalciferol on a unit basis, and may be more beneficial in reducing falls.

Conclusion

In conclusion, pharmacists need to be continually aware of the evidence for vitamin therapy in the elderly, particularly with regard to recommendations for high-dose vitamin therapy in otherwise healthy patients. Experimental and observational (non-RCT) data often do not translate into therapeutic benefits, and often well designed studies raise a number of additional safety concerns. This was well documented with a recent systematic review of high-dose antioxidants finding that, contrary to previous observational data, not only high-dose beta-carotene, vitamin A and vitamin E did not reduce the risk of mortality, but that they may actually increase mortality risk. This theme is followed in some of the examples discussed here: high-dose B-group vitamins do not seem effective in the prevention of cardiovascular disease and may even accelerate progression of cardiovascular disease in certain patients. The benefits of B-group vitamin supplementation for cardiovascular disease, stroke and dementia are also limited in the presence of adequate dietary folate intake. Calcium supplementation has also recently come under question in healthy elderly women due to a possible increased risk of myocardial infarction. There seems to be little likelihood for causing harm when patients are either deficient in certain vitamins, and are supplemented at doses at or below the recommended daily intake.

Some authors have suggested that all adults would benefit from taking a basic multivitamin on the basis that most people do not consume an optimal amount of vitamins by diet alone. The various nutritional challenges in the elderly population also seem to support this concept. At present there appear to be few indications for high-dose or mega-dosing of vitamins in the elderly. Even in fracture and fall prevention in the elderly, it tends that patients are who deficient in calcium or vitamin D who tend to benefit most from supplementation; patients with a dietary intake nearer to normal seem to face a reduction in benefit and an increase in the risk of adverse effects from high-dose supplementation of calcium.

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References