# Caution with complementaries for cognitive impairment

***Ken Harvey**, Adjunct Senior Lecturer, School of Public Health, La Trobe University, and **Con Stough**, Professor of Neuropsychology, Brain Sciences Institute, Swinburne University, Melbourne*

## Summary

**As the Australian population ages the burden of dementia is increasing. Conventional drug treatment only provides modest benefits for patients, so patients and their carers often turn to complementary medicines. Early trials showed promise for some compounds but larger better conducted studies have usually failed to confirm these benefits. However, there have been few large-scale interventions using complementary medicines for cognition. Health professionals should always ask patients (and their carers) if complementary medicines are being taken because adverse effects and interactions with conventional drugs can occur.**

Key words: dementia, *Ginkgo biloba*, vitamin E.

*(Aust Prescr 2011;34:19–21)*

## Introduction

In Australia around 200 000 people currently have dementia, including up to half of all patients in residential aged-care facilities. Given the projected rise of Australia's aged population, these numbers are likely to double in the next 20 years.[1]

Conventional drug treatment only provides modest benefits to patients with dementia and does not modify the underlying pathological progression. Patients and their carers may turn to complementary medicines, but this course of action is not without risk. Research by the National Prescribing Service (NPS) has shown that almost half the consumers surveyed had not discussed their use of complementary medicines with their doctors. Similarly, only half the general practitioners surveyed had asked their patients if they took these medicines. In addition, many general practitioners and pharmacists were unaware of the adverse effects of commonly used complementary medicines and their potential interactions with conventional medicines.[2]

## Quality and safety

One of the main concerns with herbal products is variation in their active components, not all of which are known or standardised by regulation. A specific herbal product that has been shown to be efficacious in clinical trials may be materially different from another sold under the same name by another company. Patients (and carers) should ask whether the specific brand of complementary medicine they are considering buying has been clinically trialled. They should also check for an Aust L (listed) or Aust R (registered) number on the pack.[3]

A listed product only meets the standards of the Australian Therapeutic Goods Administration (TGA) for good manufacturing practice, while a registered product has clinical evidence which has been assessed to show that the product is efficacious.[3] Most complementary medicines are listed products and the TGA does not usually check the claims made for these products.

Perhaps the most important issue surrounding the use of herbal medicines is patient safety. While listed products are regarded by the TGA as 'relatively low risk', their safety has usually not been systematically studied in the same manner as it is for registered pharmaceutical products. There are few large-scale trials and they rarely assess safety as well as efficacy. It is difficult to make confident predictions about safety and most information comes from single case studies. Until systematic evidence emerges from carefully controlled studies, physicians should adopt cautious strategies in treating and advising patients who take complementary medicines, particularly if there are known herb–drug interactions.

## Ginkgo biloba

There are 122 products whose name contains *Ginkgo biloba* listed on the Australian Register of Therapeutic Goods (ARTG). It is one of the commonest herbal medicines taken to prevent or treat cognitive impairment. Claims include, 'helps to improve blood flow to the brain' and 'improves memory and cognitive function'. There is some evidence that taking ginkgo leaf extract orally modestly improves symptoms of Alzheimer's, vascular, or mixed dementias, but this comes from poor quality studies.[4]

A study, funded by the US National Center for Complementary and Alternative Medicine, of the well-characterised ginkgo product EGb-761 found it ineffective in lowering the overall incidence of dementia and Alzheimer's disease in the elderly. Further analysis also found ginkgo to be ineffective in slowing cognitive decline. This trial recruited more than 3000 volunteers aged 75 and over who took 240 mg of ginkgo daily, and followed them for around six years.[5,6] Some smaller studies for

memory enhancement have had promising results, but a trial sponsored by the US National Institute on Aging of more than 200 healthy adults over age 60 found that ginkgo taken for six weeks did not improve memory.[7]

A recent press release reports that the IPSEN GuidAge study, involving 2854 participants aged 70 years or older complaining of memory problems, showed a statistically significant decrease in progression to Alzheimer's disease. The study authors conclude that the difference between their results and those of the earlier US study is due to differences in compliance.[8] At this stage the results should be treated with caution as they have not yet appeared in a peer-reviewed publication.

Adverse effects of ginkgo can include headache, nausea, gastrointestinal upset, diarrhoea, dizziness, or allergic skin reactions. Severe allergic reactions have occasionally been reported. There are case reports suggesting that ginkgo can increase the risk of bleeding.[9] It is therefore recommended that patients be cautioned if they take aspirin, warfarin or other antiplatelet or anticoagulant drugs, have bleeding disorders, or are expecting to have surgical or dental procedures.[4]

## Vitamin E

A variety of antioxidants and free radical scavengers including vitamin E have been promoted for use in Alzheimer's disease. A recent Cochrane review concluded there is no evidence of efficacy of vitamin E in the prevention or treatment of Alzheimer's disease.[10] While oral vitamin E seldom causes immediate adverse effects, another Cochrane review suggested that vitamin E supplementation may increase mortality.[11]

## Brahmi and Gotu Kola

There are 32 products on the ARTG whose names include *Bacopa monnieri* (Brahmi) or *Centella asiatica* (Gotu Kola) often combined together, with or without *Ginkgo biloba*. Claims include, 'traditional Asian and Ayurvedic herbs in a triple action synergistic formula to help improve memory retention, learning, concentration, alertness'. There is increasing evidence that standardised extracts of Brahmi, administered for at least three months, improve some aspects of cognition in healthy people but these observations need to be replicated in larger trials. A recent comprehensive review of the effect of bacopa extract on cognition in healthy people reported that of the seven known chronic trials in this area all showed significant cognitive improvements (Stough, unpublished, 2011).

There are no published randomised controlled trials of these herbs in dementia, either alone or in combination. A recent open-label study, in which five patients with Alzheimer's disease were given 300 mg of bacopa extract for six months,[12] found that four improved their Mini Mental State Examination scores and three improved on the Alzheimer's Disease Assessment Scale–cognitive subscale. Clearly, larger randomised double-blind trials are required.

While adverse effects appear uncommon, there have been three cases of hepatotoxicity associated with Gotu Kola.[13] There are some reports of changes in bowel function with bacopa extract.[12]

## Acetyl-L-carnitine

There are 26 products containing acetyl-L-carnitine listed on the ARTG. They make claims such as, 'helps maintain healthy cognitive function and memory during ageing' and 'may provide protective effects against age related processes and neurodegeneration'. Acetyl-L-carnitine is structurally related to acetylcholine and it was thought it might act as an analogue of acetylcholine in patients with Alzheimer's disease. While some trials have reported positive results, a 2003 Cochrane review concluded there was 'no evidence of benefit of acetyl-L-carnitine for dementia'.[14] Orally, acetyl-L-carnitine is generally well tolerated although it may cause nausea, vomiting, gastrointestinal upset and agitation. One of its metabolites can cause the urine, breath and sweat to have a fishy odour. Acetyl-L-carnitine should be used cautiously if the patient is taking warfarin.[15]

## Other products

There are other products promoted for cognitive enhancement on internet sites that are not listed or registered on the ARTG. These include drugs such as vinpocetine and huperzine A sourced from overseas. Patients should be warned that products obtained from these sites are likely to be sub-standard, adulterated and dangerous. There are also homeopathic formulations of dehydroepiandrosterone (DHEA) available from Australian pharmacies, health food shops and internet sites. This product is promoted for 'slowing down the ageing process'. Complaints that these preparations are neither efficacious nor in accord with homeopathic tradition have been upheld by the Complaints Resolution Panel;[16] however, similar claims continue to be made.[17]

## Conclusion

Complementary medicines should always be included in a medication history of a patient with dementia. A non-judgemental discussion of risks and benefits should be informed by reputable sources of independent information. Possible adverse events should be reported. Patients and their carers should be told never to purchase medicines that lack an Aust L or Aust R number as the quality and safety of these products cannot be assured.

## References


1. O'Halloran J, Britt H, Valenti L. General practitioner consultations at residential aged-care facilities. Med J Aust 2007;187:88-91. www.mja.com.au/public/issues/187_02_160707/oha10417_fm.html [cited 2011 Jan 5]

2. National Prescribing Service. Complementary medicines information use and needs of health professionals: general practitioners and pharmacists. Sydney: NPS; 2008, updated 2009. www.nps.org.au/__data/assets/pdf_file/0020/66620/CMs_Report_-_HP_-_Apr_09.pdf [cited 2011 Jan 5]
3. Medicines Safety Update. Aust R and Aust L numbers – why are they important? Aust Prescr 2010;33:80-3.
4. Natural Medicines Comprehensive Database: Ginkgo. Therapeutic Research Faculty, Stockton (CA). http://naturaldatabase.therapeuticresearch.com [cited 2011 Jan 5]
5. DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA 2008;300:2253-62.
6. Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, et al. Ginkgo biloba for preventing cognitive decline in older adults: a randomized trial. JAMA 2009;302:2663-70.
7. Solomon PR, Adams F, Silver A, Zimmer J, DeVeaux R. Ginkgo for memory enhancement: a randomized controlled trial. JAMA 2002;288:835-40.
8. IPSEN. Encouraging results of a GuidAge, large scale European trial conducted in the prevention of Alzheimer's dementia [press release]. 2010 Jun 22. www.pharmiweb.com/pressreleases/pressrel.asp?ROW_ID=24073 [cited 2011 Jan 5]
9. Bent S, Goldberg H, Padula A, Avins AL. Spontaneous bleeding associated with *ginkgo biloba*: a case report and systematic review of the literature. J Gen Intern Med 2005;20:657-61.
10. Isaac MG, Quinn R, Tabet N. Vitamin E for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev 2008; 3.
11. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst Rev 2008; 2.
12. Morgan A, Stevens J. Does Bacopa monnieri improve memory performance in older persons? Results of a randomized, placebo-controlled, double-blind trial. J Altern Complement Med 2010;16:753-9.
13. Natural Medicines Comprehensive Database: Gotu Kola. Therapeutic Research Faculty, Stockton (CA). http://naturaldatabase.therapeuticresearch.com [cited 2011 Jan 5]
14. Hudson SA, Tabet N. Acetyl-l-carnitine for dementia. Cochrane Database Syst Rev 2003; 2.
15. Natural Medicines Comprehensive Database: Acetyl-L-carnitine. Therapeutic Research Faculty, Stockton (CA). http://naturaldatabase.therapeuticresearch.com [cited 2011 Jan 5]
16. Complaints Resolution Panel Determination. Complaint 9-0507(1). Homoeopathic DHEA. 2007 Oct 4. www.tgacrp.com.au [cited 2011 Jan 5]
17. Organics Australia Online. Blue Roc – Optigen DHEA 3 mg 90 tablets (Homeopathic preparation). www.organicsaustraliaonline.com.au/prod5491.htm [cited 2011 Jan 5]

*Dr Harvey has provided advice to sponsors and industry associations involved with complementary medicines. Professor Stough has been the recipient of research grants from Flordis Medicines studying bacopa and cognition.*

# Valediction

## John Tiller

Professor John Tiller retired as the chairman of the Editorial Executive Committee of *Australian Prescriber* at the end of 2010. This concluded a long association with the journal, beginning in 1992 when he stood in for a colleague on sabbatical leave for a year. Professor Tiller joined the Committee as a full member in 1995 and became the chairman in 2005.

Although Professor Tiller's primary interest is psychiatry, he has contributed greatly to the discussion of other therapeutic topics. His sense of humour has helped the Editorial Executive Committee through its considerable workload. Tiller's travel tales have been particularly entertaining.

Perhaps because of his extensive involvement in research, Professor Tiller is a firm believer in the importance of independent information about therapeutics. He has been a strong supporter and advocate for *Australian Prescriber* and has represented the journal well. The Editorial Executive Committee has appreciated this enthusiasm and looks forward to Professor Tiller's continuing support.