



# Therapeutics Today

*Nollaig Shona dár léitheoirí go léir!  
Happy Christmas to all our readers!*



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**Time to forget Ginkgo?** Effective treatments for the prevention or delay of onset of dementia are lacking. The herb *Ginkgo biloba* is used in some parts of the world for its potential effects on memory and cognition; however there has been little research assessing its effect in the primary prevention of dementia. One of the major mechanisms by which it is thought to exert its effect is by the action of multiple antioxidants and research recently suggested that it may have an anti-amyloid aggregation effect. The results of a randomised controlled trial, which assessed the effectiveness of *G biloba* in reducing the incidence of all-cause dementia and Alzheimer's Disease (AD) in elderly people with normal cognition and those with mild cognitive impairment (MCI) was recently published (*JAMA 2008; 300: 2253-2262*). Volunteers (n=3072 aged  $\geq 75$  yrs) in 5 US academic centres, with normal cognitive function or MCI were randomised to 240mg of *G biloba* extract or an identical placebo and followed up for a median of 6.1 years. The two primary outcomes were all-cause dementia and AD, which were determined by expert panel consensus. The study found that there was no significant difference between the two groups for the emergence of dementia or AD: the hazard ratio (HR) for *G biloba* vs. placebo for all cause dementia was 1.12 (95% confidence interval [CI], 0.94-1.33; P=0.21) and for AD, 1.16 (95% CI, 0.97-1.39; P=0.11). *G biloba* also had no effect on the rate of progression to dementia in participants with MCI. There were no significant differences in the rate of serious adverse events between the two groups. The authors of the study concluded that *G biloba* was not effective in reducing the overall incidence of dementia or AD in elderly individuals with normal cognition or those with MCI.



**A big thank-you from us to you!** The NMIC would like to thank all those GPs who took the time to take part in our recent survey, which sought to elicit their opinion on the usefulness of the NMIC bulletins and Therapeutics Today (TT) newsletters as educational tools. Although there was a low response rate of 21% to the survey, the respondents (n=481) were representative of the GP population as a whole. The majority of the respondents regarded the publications (bulletins 91% and newsletters 83%) useful as educational tools; however there did appear to be a perception that the bulletins were more highly regarded than the newsletters. While the majority of respondents were also satisfied with the content and format of the publications (bulletins 95% and newsletters 91%), we received some useful comments as to how they can be improved. The respondents also reported that, in addition to the publications being used for their own continuing medical education, they are also used for additional educational activities (with peers and students), and in their everyday practice. Of interest, the respondents reported that a wide variety of other educational sources influence their prescribing including: journals, courses/meetings and the internet.

We received some valuable suggestions for therapeutic areas to be covered in future bulletins, some of which we have already used. We are also considering additional ways to improve the publications, based on the comments we received. We would like to remind our readers that **previous editions of the bulletins and newsletters are available on our website on [www.nmic.ie](http://www.nmic.ie)** or they can be posted or e-mailed directly on request.

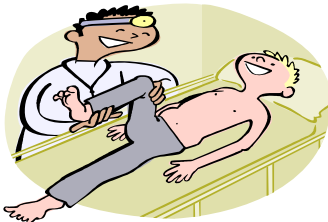
Our door is always open for more comments on the publications and for any additional therapeutic areas that the readers would like us to cover in future publications. We also wish to remind you that in addition to the publications, **we also provide an enquiry answering service to healthcare professionals on all aspects of the therapeutic use of medicines**, which includes independent information and advice on drug interactions and adverse effects, drug use in pregnancy, breastfeeding, liver and renal impairment, identification of medicines and information on sourcing of medicines.

A big **THANK-YOU** once again to all the respondents and may we wish all our readers a very happy Christmas and very best wishes for 2009!



**Go easy on the (cranberry) sauce!** A case report of a patient on warfarin experiencing an increase in INR after eating cranberry sauce was recently published (*Am J Health-Syst Pharm* 2008; 65: 2113-6). The 75-year-old Caucasian man had been on 22.5mg/week warfarin with a stable INR (between 2-3) for the previous 10 months. He was also taking calcium carbonate, cholecalciferol, digoxin, metoprolol, simvastatin and furosemide. His medical history included: atrial fibrillation, benign hypertension, hyperlipidaemia, vitamin

B12 deficiency and cerebrovascular disease. Shortly after Thanksgiving the patient's INR was found to be 4.8, which was not associated with any bleeding or bruising. The patient had a previous history of alcohol abuse, however he denied alcohol consumption, any recent change in medication or intake in nutritional supplements, which was confirmed by his wife. The patient did however admit to eating a turkey sandwich with 113g shop-bought cranberry sauce each day for the preceding week. The patient's warfarin was withheld for 2 days and seven days after he discontinued the cranberry sauce, his INR had returned to 2.2. Evaluation of this report suggested a possible causal relationship between consumption of cranberry sauce and potentiation of warfarin (with elevated INR). The interaction between cranberry juice and warfarin has been published but this appears to be the first report of an interaction between cranberry sauce and warfarin.



**Statin-induced myopathy.** It is estimated that >100 million prescriptions/year are dispensed globally for statins and that 1.5 million people/year will experience a muscle-related event while taking a statin. A recent paper reviewed statin-induced myopathy (*BMJ* 2008; 337: 1159-62). Statin-induced myopathy includes **myalgia** (symptoms with normal creatine kinase (CK)), **myositis** (symptoms and CK <10 X upper limit of normal (ULN)) **rhabdomyolysis** (symptoms and CK >10 X ULN) and an **asymptomatic increase in**

**CK.** Symptoms include fatigue, muscle pain, tenderness or weakness, nocturnal cramping and tendon pain. Muscle symptoms tend to be proximal, generalised and worse with exercise. Reported treatment duration has ranged from one week to four years before onset of myopathy, although muscle symptoms developing in a patient taking a statin for several years are unlikely to have been caused by the drug per se. The mechanism of action is unknown but risk factors include statin dose, advanced age, female gender, low BMI, hepatic or renal dysfunction, co-morbidities and drug interactions, excess alcohol or dietary effects. **Any factor that increases the serum concentration of a statin has the potential to increase the risk of myopathy.** *In vitro* and *in vivo* experiments suggest that lipophilic statins (e.g. simvastatin, atorvastatin) may be more likely to produce muscle effects than the relatively hydrophilic agents (e.g. pravastatin, rosuvastatin) but there is no large direct comparison study available. Guidelines vary for checking baseline CK but it is **reasonable to measure baseline CK in high-risk groups. Similarly, on treatment, CK monitoring is recommended if the patient becomes symptomatic or if an interacting drug is added.** If a patient presents with muscle pains, other possible causes should be ruled out (e.g. muscle strain, osteoarthritis, tendonitis, bursitis). Serum CK and TSH should be checked (hypothyroidism is a cause of elevated CK and raised cholesterol and predisposes to statin-induced myopathy). Patients with tolerable symptoms and CK <10 X ULN may continue treatment but should be closely monitored to ensure the condition is not progressive. [Many experts recommend in this case that if CK is >3 X ULN consideration should be given to reducing dose or changing to a less potent statin if the LDL target has been met]. When CK is very high, the drug should be stopped immediately and the patient's renal function and urinary myoglobin (seen with rhabdomyolysis) checked. Statin therapy should be stopped in patients with tolerable symptoms but CK >10 X ULN; the benefits and risks should be reviewed - an alternative class of agent might be used or the statin / another statin re-introduced at a lower dose at a later date. Patients with atypical findings should be referred for specialist advice.

[**Editor's note:** a recent paper identified genetic variants that may be associated with increased risk of statin-induced myopathy, which hopefully will enable safer use in the future (*NEJM* 2008; 359: 789-99). In the September TT newsletter, we reminded prescribers that the risk of myopathy seems to be particularly affected by drug interactions and deaths have been reported in Ireland. **When considering concomitant therapy with a statin, prescribers are advised to look at the SPC for each medicine to get all available information on potential interactions. Check out [www.imb.ie](http://www.imb.ie); or [www.medicines.ie](http://www.medicines.ie)**]