

- Heart Outcomes Prevention Evaluation (HOPE) Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy [published correction appears in *Lancet* 2000; 356: 860]. *Lancet* 2000; 355: 253-259.
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IN REPLY: Peverill raises the question of how to integrate the new data on renal protection by angiotensin II receptor (AIIR) antagonists with existing data on cardiovascular protection by angiotensin-converting enzyme (ACE) inhibitors in patients with type 2 diabetes. An AIIR antagonist would be favoured for renal protection for a diabetic patient with hypertension and evidence of early or overt nephropathy. With regard to patients with microalbuminuria, the HOPE and MICRO-HOPE studies showed that therapy with the ACE inhibitor ramipril (10 mg/day) was associated with a 24% relative risk reduction for the development of overt nephropathy over 4.5 years.¹ In contrast, treatment of similar patients with the AIIR antagonist irbesartan (300 mg/day) for 2.6 years resulted in a 70% risk reduction for the development of overt nephropathy.² Use of an AIIR antagonist in patients with overt nephropathy has also been shown to slow progression to end-stage renal failure.^{3,4} As the HOPE and MICRO-HOPE studies specifically excluded such patients, evidence supporting use of an ACE inhibitor in this context is lacking.

An ACE inhibitor could be used if a diabetic patient has microalbuminuria and a history of coronary heart disease or additional risk factors for cardiovascular disease, especially if normotensive. However, almost all patients with microalbuminuria require antihypertensive therapy as well as therapy to protect target organs. The relative importance of blood-pressure-lowering versus non-lowering effects of antihypertensive therapy on reducing risk of cardiovascular disease remains uncertain.⁵ Furthermore, a recent meta-analysis of cardiovascular protection in 62 605 patients

with hypertension (including the HOPE and United Kingdom Prospective Diabetes studies) did not find that ACE inhibitors affected cardiovascular prognosis beyond their antihypertensive effects.⁶

Finally, it is important to note that neither ACE inhibitors nor AIIR antagonists provide total protection from cardiovascular and renal events, and that further improvements are needed for both microvascular and macrovascular protection in patients with type 2 diabetes.

- Heart Outcomes Prevention Evaluation (HOPE) Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; 355: 253-259.
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Pharmacological treatment of cognitive deficits in Alzheimer's disease

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TO THE EDITOR: The review by Brodaty and colleagues¹ on drug treatment of Alzheimer's disease provides a good, concise and balanced overview. However, Pfizer takes issue with some of the referenced safety data.

In Box 3 of that article (Profiles of cholinesterase inhibitors), in reference to adverse effects of donepezil (Aricept, Pfizer), it is stated that "At 10 mg/day, nausea (17% of patients), diarrhoea (17%) and vomiting (10%) may occur.⁴⁹" Reference 49 at this point appears to be an incorrect citation.

The figures of 17%, 17% and 10% for nausea, diarrhoea and vomiting, respectively, appear to have been taken from an article by Rogers and Friedhoff.² It is important to note that this was a non-comparative, open-label extension study, and these incidences of gastrointestinal adverse events are inconsistent with data presented in the Australian Product Information for donepezil,³ which quote rates of

nausea, diarrhoea and vomiting of 11%, 10% and 5%, respectively. These incidences are derived from a patient cohort of 1102 patients who participated in appropriately designed comparative (active and placebo) pre-registration studies of donepezil. These data have recently been confirmed in a one-year, randomised, placebo-controlled study of donepezil in patients with mild to moderate Alzheimer's disease.⁴ Incidences of 11.3%, 7.0% and less than 5% for nausea, diarrhoea and vomiting, respectively, are quoted in that study.

We contend that, while the citation referenced by Brodaty et al was incorrect, the figures quoted for the gastrointestinal safety incidences for donepezil are also inconsistent with the Product Information and current published data.

- Brodaty H, Ames D, Boundy KL, et al. Pharmacological treatment of cognitive deficits in Alzheimer's disease [review]. *Med J Aust* 2001; 175: 324-329.
- Rogers S, Friedhoff L. Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: an interim analysis of the results of a US multicentre open label extension study. *Eur Neuropsychopharmacol* 1998; 8: 67-75.
- Australian-approved Product Information for Donepezil. Sydney: Pfizer Pty Limited, 10 December 2001.
- Winblad B, Engedal K, Soininen H, et al and the Donepezil Nordic Study Group. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 2001; 57: 489-495. □

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IN REPLY: We thank Lam for pointing out an error in the referencing in Box 3 of our article¹ regarding the figures for adverse events for donepezil. The correct reference was number 48 in our list, not 49, and was to Rogers, Farlow, Doody et al,² not to Rogers and Friedhoff,³ as suggested by Lam. The other references in Box 3 were given as 20, 21, 23 and 48, but should have been listed as 19, 20, 21 and 47, respectively.

Secondly, issue is taken with the rates of 17%, 17% and 10% for nausea, diarrhoea and vomiting, respectively, in people taking donepezil. We agree with the overall tenor of this letter that rates of side effects are generally lower in everyday practice.

The figures we quoted for adverse events are higher than the 11%, 10% and 5% cited

in the Australian Product Information for donepezil,⁴ as the article by Rogers and colleagues² refers to rates of adverse events experienced by those on the 10 mg dose, after a forced titration after *only* one week on 5 mg. We presented data for adverse events at the 10 mg dose, as this was the dose recommended for donepezil given the findings of greater benefit on the higher dose. The Australian Product Information does not indicate whether the rates of adverse events refer to the 5 mg or 10 mg dose.

Usual clinical practice, which is to start with 5 mg daily and increase to 10 mg after 4–6 weeks, results in fewer adverse events. The figures of 11.3% for nausea, 7% for diarrhoea and less than 5% for vomiting presented in the Nordic study,⁵ in which over 80% of patients were taking 10 mg of donepezil daily, with a more flexible titration schedule, appear to be more realistic.

1. Brodaty H, Ames D, Boundy KL, et al. Pharmacological treatment of cognitive deficits in Alzheimer's disease [review]. *Med J Aust* 2001; 175: 324-329.
2. Rogers SL, Farlow MR, Doody RS, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998; 50: 136-145.
3. Rogers S, Friedhoff L. Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: an interim analysis of the results of a US multicentre open label extension study. *Eur Neuropsychopharmacol* 1998; 8: 67-75.
4. Australian-approved Product Information for Donepezil. Sydney: Pfizer Pty Limited, 10 December 2001.
5. Winblad B, Engedal MD, Soininen H, et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 2001; 57: 489-495. □

High prevalence of coeliac disease in a population-based study from Western Australia: a case for screening?

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TO THE EDITOR: I read with interest the recent article by Olynyk's group at Fremantle on the prevalence of coeliac disease in rural Western Australia.¹

It is now increasingly realised that coeliac disease is underdiagnosed in adults because it may be clinically silent — but not necessarily asymptomatic. The symptoms, however, may be non-specific and not those traditionally associated with coeliac disease. In a recently reported small study from suburban Melbourne,² I demonstrated that about 5% of patients (5/97) undergoing gastroscopy had coeliac disease based on small-bowel biopsy results. In only one of

the patients was the disease suspected clinically.

I have used these figures to argue the case for routine duodenal biopsy at the time of gastroscopy, regardless of the indication. It is important to note that in my study none of the patients presenting with diarrhoea, and only one of six with anaemia, had coeliac disease — so that restricting biopsy to this group would have missed most patients with coeliac disease.

Timely diagnosis is important, as symptoms may be alleviated, presymptomatic nutritional deficiencies corrected, and the risk of cancer reduced by instituting a gluten-free diet. People presenting for gastroscopy represent a high-yield group for histological screening for coeliac disease in Australia.

1. Hovell CJ, Collett JA, Vautier G, et al. High prevalence of coeliac disease in a population-based study from Western Australia: a case for screening? *Med J Aust* 2001; 175: 247-250.
2. Ryan J. Case 5-2001: Unsuspected coeliac disease [letter]. *N Engl J Med* 2001; 344: 1950-1951. □

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IN REPLY: We agree with Ryan that coeliac disease is common in the Australian community, with a prevalence of 1 in 250.¹ Furthermore, all individuals positive for antiendomysial antibody who undergo small-bowel biopsy have typical features of coeliac disease.¹ Clearly, there is a need to increase awareness relating to coeliac disease and determine appropriate screening strategies for our population.

Ryan suggests that patients presenting for upper gastrointestinal endoscopy represent a group in whom a high diagnostic yield of coeliac disease is expected.² However, clinical expression of the disease is variable.¹ In this setting, we believe that it is important to determine the cost-effectiveness of the various screening strategies before introducing broad-based screening.³ There is no doubt that treatment of symptomatic patients who present with coeliac disease is appropriate, but there are limited data on outcomes for asymptomatic patients who are discovered in population-based screening programs.

As we stated in our article, we recommend screening by serology and small-bowel biopsy if the clinical suspicion is high or the patient is in a high-risk group.

1. Hovell CJ, Collett JA, Vautier G, et al. High prevalence of coeliac disease in a population-based study from Western Australia: a case for screening? *Med J Aust* 2001; 175: 247-250.
2. Ryan J. Case 5-2001: unsuspected coeliac disease [letter]. *N Engl J Med* 2001; 344: 1950-1951.
3. Navab F. Case 5-2001: unsuspected coeliac disease [letter]. *N Engl J Med* 2001; 344: 1951-1952. □

Megadose vitamin C in treatment of the common cold: a randomised controlled trial

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TO THE EDITOR: There is much conflicting evidence that increased intake of vitamin C enhances the natural protective mechanisms of the body and decreases both the incidence and severity of the common cold.¹

It is regrettable that the study by Audera and colleagues failed to show a significant therapeutic effect of megadose vitamin C in treatment of the common cold.² The groups compared had, on average, similar composition after randomisation. However, the viral infections that cause the common cold and its progression to ill health, as evidenced by multiple symptoms, are affected by many factors, while symptom severity is well known to vary greatly. Therefore, the study's reliance on respondents' self-diagnosis of symptom severity and onset is a significant weakness in design.

Randomisation of participants to the treatment groups may have been insufficient to override this design deficit, thereby significantly biasing the outcome. A better design might have combined patient self-report of symptom severity with physical examination, thus allowing independent and professional assessment of severity. Also, proper assessment of previous history of severity of cold symptoms is crucial for proper randomisation to treatment groups. If Audera and colleagues' study failed to control for this history, then randomisation may have also failed to balance its effect equally between treatment groups, significantly compromising the study's validity to detect any therapeutic benefit of vitamin C. Cold symptoms also vary diurnally, while severity varies with alcohol use and smoking status,^{3,4} which also affect vitamin C absorption.^{5,6} No information was provided on study participants' alcohol consumption and smoking status.