

Is bupropion (Zyban) causing deaths?

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TO THE EDITOR: From 1 February to 30 June 2001, 277 602 prescriptions for the smoking cessation drug bupropion hydrochloride (Zyban, GlaxoSmithKline) were processed. The Health Insurance Commission approved 343 737 prescriptions for bupropion between 1 February and 30 June.¹ Comparing this figure with the 277 602 processed scripts, some 66 135 (19.2%) scripts went unfilled. One reason for this may have been extensive publicity given to reports of deaths and numerous adverse reactions following bupropion use.

The website of the Australian Drug Reactions Advisory Committee (ADRAC) reports that, as at 22 June, there had been 18 reports of deaths in patients aged from 30 years to 69 years who were using or who had recently stopped using bupropion.² ADRAC summarised intelligence on these deaths thus:

... there were a variety of reported causes of death and not a single consistent mode of death. In addition to being smokers, several patients had other existing risk factors for unexpected death such as alcohol abuse, diabetes or cardiomyopathy. Eleven of the 18 patients had an alternative explanation for death that was at least as plausible as a possible effect of bupropion. In four reports, the available information was very limited and it was not possible to assess the cause of death. Further information is being sought on three cases to aid assessment of the cause of death.²

Smokers are at 3.1 times greater risk of dying (from any cause) than non-smokers and twice as likely to die from coronary disease and stroke.³ People with depression are three times as likely to be daily smokers⁴ and have double the suicide rate of non-smokers.⁵

In Australia, sudden coronary fatalities occur at a rate of about 450 per million people aged under 65,⁶ perhaps at a rate of 355 per million in non-smokers and about double that in smokers. In three months (the period of recommended bupropion use), one would expect 180 deaths per million smoker-users. Thus, among 277 602 Australian smokers, 50 might die during any given three-month period without any added risk from bupropion.

This estimate helps to place the 18 fatalities reported to ADRAC in context.

The 277 602 scripts represent about 9.5% of Australia's 2.9 million regular smokers. These people, their families and doctors deserve to have their anxieties about the risks of using bupropion addressed. We would urge the government to commission urgently a case-control study of morbidity and mortality among smokers and their relationships to use or non-use of bupropion.

Competing interests: SC has received funding from SmithKlineBeecham (now GlaxoSmithKline) for the preparation of professional and public educational material on smoking in Australia.

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Carotid stenting or endarterectomy for stroke prevention

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TO THE EDITOR: I read with interest the article by Hender and colleagues recently published in the Journal.¹ I agree with the authors' conclusion that there is presently insufficient evidence to suggest the widespread use of endoluminal treatment for carotid artery disease. However, there are a number of problems with the authors' interpretation of our recent article

comparing the outcome of surgical and endoluminal treatment of symptomatic carotid stenosis.²

Firstly, the figures in the Box are completely misleading. The percentages of adverse outcome quoted for patients undergoing endoluminal treatment are those that were found for cases receiving endarterectomy, while the figures quoted for endarterectomy are the findings for endoluminal treatment. [A correction of this error was published in the 3/17 December 2001 issue of the Journal, page 672.] Hence, any reader simply looking at the Box would be left with the false conclusion that the outcome of endoluminal treatment is superior.

Secondly, the authors refer to our article² as a "meta-analysis". In our article we went to some trouble to explain that a meta-analysis was not possible, as only one small randomised trial had been published at that time. Instead, we had to use reports from single centres and we discussed the difficulties of comparing the results when patients had not been randomised.

Thirdly, the results of the CAVATAS trial were published in June 2001.³ A surprising finding was that the perioperative stroke rate (defined as a neurological deficit lasting seven days or more) for patients undergoing either carotid angioplasty (with or without stenting) or conventional endarterectomy was the same (around 10%). In fact, the disabling stroke rate of around 6% after either endovascular treatment or endarterectomy was three times higher than that found in the North American randomised trial of endarterectomy.⁴

Finally, the authors refer to our patients undergoing carotid *stenting*, whereas the majority of the patients referred to in fact received angioplasty alone.

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Correspondents

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Carotid stenting — current caution

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TO THE EDITOR: Carotid stenting is a new application of endovascular therapy. Its efficacy in preventing strokes is yet to be established, by contrast with the proven Level 1 evidence of benefit from carotid endarterectomy.

The risks of implanting carotid stents at present appear greater than the risks of carotid endarterectomy. An overview of carotid endarterectomies in Australia is maintained by vascular surgeons, through audits such as the ongoing Melbourne Vascular Surgeons Association Audit and the New South Wales Carotid Endarterectomy Audit. The technique of carotid stenting, the stents themselves and the brain-protective devices used during the implanting of stents are expensive and still evolving. The long-term durability of stents is unknown.

Australian vascular surgeons, neuroradiologists and neurologists are awaiting the outcome of two major international randomised trials of carotid stenting versus endarterectomy (the US Carotid Revascularization Endarterectomy versus Stent Trial and the European International

Carotid Stenting Study). These seek Level 1 evidence of the comparative risks and success of the new stenting procedures in stroke prevention and aim to document the late outcome of stenting, particularly the incidence of restenosis, which is a significant problem in other arteries after stenting.

While these definitive trials are in progress, vascular surgeons of the Royal Australasian College of Surgeons wish to add their note of caution to the reservations expressed in the NHMRC guidelines on stroke prevention¹ and the recommendations of the Australian Association of Neurologists.² A recent commentary by Spence and Eliasziw³ illustrates the disparate nature and the limitations of existing studies of carotid stenting.

We consider carotid stenting is not yet appropriate for widespread use in Australia. Experienced endovascular and neurology teams should continue to evaluate the new procedure. Stenting of symptomatic carotid atheroma should only be conducted with the consent of patients who are fully informed about stenting's known hazards and unproven status and who understand that the established treatment is carotid endarterectomy.⁴ Clinicians should audit closely the immediate outcome and long-term complications of any carotid stenting they perform.

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Content of isoflavone-containing preparations

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TO THE EDITOR: Preparations containing isoflavone phytoestrogens are widely used as an alternative therapy for treating symptoms of the menopause. Although Australian government regulations strictly control the components of alternative therapies, adherence to the stated amounts of the components in alternative therapies is not routinely assessed. Isoflavones exist in two forms — aglycone (the free form) and glycosylated or glycone (the conjugated form) — the relative proportions of which vary between preparations. As glycosylation contributes considerably to the mass of isoflavone molecules, it is relevant to consider the total amount of potentially available isoflavone in alternative therapy preparations.

Isoflavone-containing preparations which had a recommended daily dose on their labels were purchased at random from pharmacies around Sydney during September 1999. Where possible, products from more than one manufacturing batch were purchased and all products were well within their stated shelf life. The tablets, capsules or powder were removed from their packaging to conceal their identity and randomly allocated to numbered plastic bags by the hospital pharmacy department. The samples were then sent to PhytoChem Technologies Inc (Chelmsford, Mass,

Actual and stated isoflavone content of commercially available preparations

Manufacturer	Product	No. of batches assayed	Stated isoflavone content (mg) in recommended daily maximum dose of product	Actual total isoflavone content per daily dose (mg)	Estimated aglycone isoflavone content per daily dose (mg)
Blackmores	Phytolife one a day	5	40	41.02 ± 6.12	25.75 ± 6.04
Bioglan	Soy powder plus	4	68	48.75 ± 1.42	30.44 ± 0.86
Earths Own	Soy + calcium	1	68	42.52	25.67
Health Direction	Femme phase	1	235 mg soy protein*	0.29	0.20
Herron	Phyto source	1	22.5	16.27	9.93
Natural Nutrition	Menopause	1	60	0.56	0.51
Natural Nutrition	Phytobalance	3	90	58.12 ± 6.26	34.96 ± 3.79
Novogen	Promensil	4	40	40.12 ± 1.98	38.38 ± 1.20
Pretorius	Maxi soy plus red clover wild yam and calcium	4	68	50.36 ± 1.64	31.24 ± 1.13
Wagner Probiotics	Femme soy plus with red clover	2	27	30.76 ± 0.12	19.65 ± 0.05

* Soy protein has a high isoflavone content.

Values are the mean ± standard deviation. Total isoflavones = glycone plus aglycone. Estimated available aglycone isoflavones = weight of aglycone isoflavones plus weight of glycone isoflavones corrected for glycone content.