

200 mL bottle and contained a mixture of the fluid extracts of *Nepeta hederacea* (ground ivy) 80 mL, *Hydrastis canadensis* (golden seal) 20 mL, *Ginkgo biloba* (ginkgo) 40 mL, *Avena sativa* (oats seed) 40 mL and *Cimicifuga racemosa* (black cohosh) 20 mL. According to the information supplied by the pharmacist, one gram of herb was contained in each 1 mL of extract, with the exception of golden seal, for which 0.5 g of herb was contained in each millilitre. The oats seed fluid extract was supplied by Southern Cross Herbal School (Gosford, NSW), and all other fluid extracts were supplied by the Herbal Extract Company of Australia (Sydney, NSW). The patient took a total of 600 mL over the 3-month period (7.5 mL bd orally as required). Before developing symptoms of liver failure, the patient had taken no other medications and had no risk factors for the acquisition of viral hepatitis.

On arrival, she was deeply jaundiced but not encephalopathic. Liver span was reduced and there were no signs of chronic liver disease. The international normalised ratio was 3.0 (normal, 1.0–1.2), and she had serum concentrations of albumin, 26 g/L (normal, 35–50 g/L); bilirubin, 368 $\mu\text{mol/L}$ (normal, < 18 $\mu\text{mol/L}$); alkaline phosphatase, 230 U/L (normal, 35–104 U/L); alanine aminotransferase, 1380 U/L (normal, < 55 U/L); and γ glutamyl-transpeptidase, 134 U/L (normal, < 45 U/L). Extensive investigation excluded other recognised causes of acute liver failure.

Her condition deteriorated over the following week, with the development of hepatic encephalopathy and hepatorenal failure. She underwent liver transplantation in early February 2003, and had an uneventful postoperative course. Examination of the explanted liver revealed massive hepatic necrosis.

Following transplantation, the pharmacist supplied samples of the individual extracts to the Therapeutic Goods Administration (Canberra) for analysis. The analysis revealed no undeclared pharmaceutical drugs. Assay of the individual extracts of golden seal, ginkgo and black cohosh revealed the listed ingredients to be present. The presence of ground ivy and oats seed in the extracts has not yet been confirmed owing to the lack of a suitable reference standard.

It is not possible to determine the individual ingredient, or mixture of ingredients, that resulted in acute liver failure in this patient. However, this is the third case of acute liver failure associated with black cohosh ingestion to be reported recently in Australia.¹ In this instance, liver failure progressed despite cessation of the herbal therapy, and transplantation was required, suggesting that a process of irreversible liver injury had been initiated before treatment was ceased. It should be noted that ground ivy contains pulegone, a known hepatotoxin. However, the concentration of pulegone in ground ivy is accepted to be vastly less than in pennyroyal, where pulegone-induced hepatotoxicity has been reported.² To our knowledge, there are no reports of golden seal, oats seed or ginkgo causing hepatotoxicity.

The popularity of herbal therapies is due in part to their perceived lack of side effects. It is important for the medical and broader community to be aware of the potential toxicity of these preparations. In any patient presenting with unexplained hepatitis it is essential to determine if there has been exposure to herbal therapies, since early cessation of treatment may be life saving.

1. Whiting PW, Clouston A, Kerlin P. Black cohosh and other herbal remedies associated with acute hepatitis. *Med J Aust* 2002; 177: 440-443.
2. Barnes J, Anderson LA, Phillipson JD. Herbal medicines. A guide for healthcare professionals. 2nd ed. Pharmaceutical Press, 2002. □

Hormone replacement therapy: to use or not to use?

Michael D Coory

Medical Epidemiologist, Queensland Health,
GPO Box 48, Brisbane, QLD 4001.
michael_coory@health.qld.gov.au

TO THE EDITOR: The randomised controlled trial associated with the Women's Health Initiative (WHI) found that long-term hormone replacement therapy (HRT) with combined oestrogen-progestin causes net harm.¹ Both the article by Baber and colleagues on HRT² and a previous editorial by Patel and colleagues³ imply that the method used to calculate the confidence intervals in the WHI report is questionable. Baber et al suggest that "a trial such as this, with multiple endpoints, should use adjusted rather than nominal confidence intervals to test individual end-

points for significance".² It is important that this issue is clarified.

In the WHI report in *JAMA*, Table 2 shows both nominal and adjusted confidence intervals for the primary and secondary outcomes.¹ Nominal confidence intervals are appropriate for the preselected primary outcomes of the trial — breast cancer, coronary heart disease and the composite global-index score.⁴ Confidence intervals adjusted for multiple comparisons are possibly appropriate for the multiple secondary endpoints in the study, but are not advocated by all statisticians.⁵ In any case, the decision of Baber and colleagues to concentrate on adjusted confidence intervals for the preselected primary outcomes is not valid.⁴

The purpose of confidence intervals is to assess the effects of random variation or chance. It is not sensible to suggest that the extra harm that occurred in the combined HRT arm of the WHI study could be due to chance. Moreover, 42% of women in the HRT group stopped taking the drug, and 11% of women in the placebo group started taking it.¹ Therefore, the reported findings of the intention-to-treat analysis underestimated the true harm to individual women taking long-term HRT. Also, if duration of treatment is important (as appears the case with breast cancer risk), and because compliance decreased over time, 5-year results underestimated longer-term treatment harm.⁴

The aim of the WHI trial was to assess whether long-term HRT is a useful preventive intervention for postmenopausal women. It did not assess the short-term use of HRT to relieve severe hot flashes. As Sackett points out, curative and preventive medicine are absolutely and fundamentally different in their obligations and implied promises to the individuals whose lives they hope to modify.⁶ As a long-term preventive intervention, HRT causes more harm than good. Although the absolute risks were small, millions of women were prescribed this treatment worldwide, causing harm to thousands. Billions of dollars were spent on an ineffective preventive intervention.⁶ The thousands of Australian women who stopped taking HRT on learning the results of the WHI trial made a sensible decision.

- Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321-333.
- Baber RJ, O'Hara JL, Boyle FM. Hormone replacement therapy: to use or not to use? *Med J Aust* 2003; 178: 630-633.
- Patel A, Norton R, MacMahon S. The HRT furore: getting the message right [editorial]. *Med J Aust* 2002; 177: 345-346.
- Fletcher SW, Colditz GA. Failure of estrogen plus progestin therapy for prevention. *JAMA* 2002; 288: 366-367.
- Perneger TV. What's wrong with Bonferroni adjustments? *BMJ* 1998; 316: 1236-1238.
- Sackett DL. The arrogance of preventive medicine. *CMAJ* 2002; 167: 363-364. □

**Rodney J Baber,* Justine L O'Hara,†
Frances M Boyle‡**

*Clinical Senior Lecturer, Department of Obstetrics and Gynaecology, University of Sydney, NSW, 2006;
†Medical Student, ‡Oncologist, Royal North Shore Hospital, Sydney, NSW. rbaber@mail.usyd.edu.au

IN REPLY: We acknowledge that not all statisticians agree on the place of adjusted confidence intervals. However, we and others^{1,2} believe they represent a conservative choice for secondary endpoints in a study with multiple endpoints, such as the WHI trial.

Results of recent randomised controlled trials of hormone replacement therapy (HRT) and cardiovascular disease certainly support the notion that HRT confers no protection. However, any real harm of HRT must be questionable in light of the rapid review by Beral and colleagues, which, also using nominal confidence intervals, showed no change in relative risk for HRT users.³

We are surprised that, having emphasised the importance of nominal confidence intervals for primary endpoints, Coory did not mention that the breast cancer risk in the WHI report was not statistically significant using either nominal or adjusted CIs, or that the global index used was a non-validated instrument designed for and used only in the WHI study.⁴ Intention-to-treat analysis is used to avoid overestimates of both harm and benefit. While drop-in and drop-out rates (equal in both arms) may have led to underestimates of harm from HRT, they may also have led to underestimates of benefit, with no net change to risk-benefit assessment.

The aim of the WHI trial was to assess the benefit or otherwise of long-term HRT on disease processes in otherwise healthy women. There seems little doubt that in the group of older, overweight, somewhat hypertensive,

women enrolled in this trial the use of HRT was not beneficial.

The aim of our article was to assess the case for and against HRT use.⁵ In reaching our conclusions, we drew on a broad range of published data, including, but not confined to, the WHI data. Our conclusions make it clear that we believe the use of HRT is primarily for short-term relief of symptoms during the menopause transition. However, we sought to defend the right of a small number of women to choose to continue HRT for long-term improvement of quality of life and symptom relief after appropriate, balanced, individualised counselling about the risks and benefits of such a decision.

We do not agree with Coory's final comment. The thousands of Australian women who stopped taking HRT on learning the results of the WHI trial did so in fear and ignorance in an environment where their physicians were unable to offer balanced counsel — hardly a formula for good medicine.

- Patel A, Norton R, MacMahon S. The HRT furore: getting the message right. *Med J Aust* 2002; 177: 345-346.
- McDonough PG. The randomized world is not without its imperfections: reflections on the Women's Health Initiative Study. *Fertil Steril* 2002; 78: 951-956.
- Beral V, Banks E, Reeves G. Evidence from randomised trials on the long term effects of hormone therapy. *Lancet* 2002; 360: 942-944.
- Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321-333.
- Baber RJ, O'Hara JL, Boyle FM. Hormone replacement therapy: to use or not to use? *Med J Aust* 2003; 178: 630-633. □

MJA Advertisers' Index

Bayer/Glaxo

Levitra p330

Health Match BC

Recruitment p389

JGRT Holdings Pty Ltd

Technopark Real Estate p384

Medacs Healthcare Services

Medical Recruitment p340

Panasonic & Telstra

Panasonic Phone System p338

Roche

Dilatrend p357

Dilatrend PI p345

Schering Pty Ltd

Diane-35 Inside front cover

Androcur-100 Inside back cover

Betaferon Outside back cover

Servier Laboratories

Coversyl PLUS p366

The Medical Journal of Australia

Editor

Martin Van Der Weyden, MD, FRACP, FRCPA

Deputy Editors

Bronwyn Gaut, MBBS, DCH, DA

Ruth Armstrong, BMed

Mabel Chew, MBBS(Hons), FRACGP, FACHPM

Ann Gregory, MBBS, GradCertPopHealth

Manager, Communications Development

Craig Bingham, BA(Hons), DipEd

Senior Assistant Editor

Helen Randall, BSc, DipOT

Assistant Editors

Elsina Meyer, BSc

Kerrie Lawson, BSc(Hons), PhD, MASM

Tim Badgery-Parker, BSc(Hons)

Josephine Wall, BA, BAppSci, GradDipLib

Proof Readers

Raymond Carroll, Christine Binskin, BSc

Editorial Administrator

Kerrie Harding

Editorial Assistant

Christine Tsim

Production Manager

Glenn Carter

Editorial Production Assistant

Melissa Sherman, BA

Librarian, Book Review Editor

Joanne Elliot, BA, GradDipLib

Consultant Biostatistician

Val Gebski, BA, MStat

Content Review Committee: Leon Bach, PhD,

FRACP; Adrian Bauman, PhD, FAFPHM; Flavia

Cicuttini, PhD, FRACP; Marie-Louise Dick, MPH,

FRACGP; Mark Harris, MD, FRACGP;

David Isaacs, MD, FRACP; Paul Johnson, PhD,

FRACP; Jenepher Martin, MEd, FRACS;

Adrian Mindel, MD, FRACP; Michael Solomon,

MSc, FRACS; Campbell Thompson, MD, FRACP;

Tim Usherwood, MD, FRACGP; Owen Williamson,

FRACS, GradDipClinEpi; John Wilson, PhD,

FRACP; Jeffrey Zajac, PhD, FRACP

Australasian Medical Publishing Co Pty Ltd

Advertising Manager: Peter Butterfield

Media Coordinator: Julie Chappell

The Medical Journal of Australia (MJA) is published on the 1st and 3rd Monday of each month by the Australasian Medical Publishing Company Proprietary Limited, Level 2, 26-32 Pyrmont Bridge Rd, Pyrmont, NSW 2009. ABN 20 000 005 854. Telephone: (02) 9562 6666. Fax: (02) 9562 6699. E-mail: amppco@amppco.com.au. The Journal is printed by Offset Alpine Printing Ltd, 42 Boorea St, Lidcombe, NSW 2141.

MJA on the Internet: <http://www.mja.com.au/>

None of the Australasian Medical Publishing Company Proprietary Limited, ABN 20 000 005 854, the Australian Medical Association Limited, or any of its servants and agents will have any liability in any way arising from information or advice that is contained in *The Medical Journal of Australia (MJA)*. The statements or opinions that are expressed in the Journal reflect the views of the authors and do not represent the official policy of the Australian Medical Association unless this is so stated. Although all accepted advertising material is expected to conform to ethical and legal standards, such acceptance does not imply endorsement by the Journal. All literary matter in the Journal is covered by copyright, and must not be reproduced, stored in a retrieval system, or transmitted in any form by electronic or mechanical means, photocopying, or recording, without written permission.

Published in 2 volumes per year.

Annual Subscription Rates for 2003 (Payable in Advance) to:

AMPCo, Locked Bag 3030, Strawberry Hills, NSW 2012

Individual Subscriptions (includes 10% GST)

Australia—\$A291.50, Medical students (Australia only)—\$A60.00

Overseas Economy Air—\$A370.00, Airmail—\$A505.00

NZ & PNG Economy Air—\$A340.00

Indexes are published every 6 months and are available on request as part of the current subscription.

Single or back issues contact: AMPCo (02) 9562 6666.

Advice to Authors—

<http://www.mja.com.au/public/information/instruct.html>

27,579 circulation as at

31 March, 2003

ISSN 0025-729X