

approach which allows industry to set its own standards.

In summary, what both New Zealand and Australia need is greater and more accessible independent consumer health information, not impossible to regulate, industry-sponsored direct-to-consumer advertising.

References

1. Anonymous. Direct to consumer advertising of prescription medicines (DTCA) – part of a well functioning democracy and economy. New Zealand Marketing Association. 2004. <http://www.marketing.org.nz/cms/News/1173> [cited 2006 Mar 8]
2. Toop L, Richards D, Dowell T. The leadership role of general practice in public health: advocating a ban of direct-to-consumer advertising of prescription drugs in New Zealand. 'Possums in the headlights?' *Br J Gen Pract* 2003;53:342-5.
3. Toop L, Richards D, Dowell T, Tilyard M, Fraser T, Arroll B. Direct to consumer advertising of prescription drugs in New Zealand. For health or for profit? Report to the Minister of Health supporting the case for a ban on DTCA. Christchurch: New Zealand Departments of General Practice, Christchurch, Dunedin, Wellington and Auckland Schools of Medicine; 2003. <http://www.chmeds.ac.nz/report.htm> [cited 2006 Mar 8]
4. Mintzes B, Barer ML, Kravitz RL, Kazanjian A, Bassett K, Lexchin J, et al. Influence of direct to consumer pharmaceutical advertising and patients' requests on prescribing decisions: two site cross sectional survey. *Br Med J* 2002;324:278-9.
5. Mintzes B, Barer ML, Kravitz RL, Bassett K, Lexchin J, Kazanjian A, et al. How does direct-to-consumer advertising (DTCA) affect prescribing? A survey in primary care environments with and without legal DTCA. *CMAJ* 2003;169:405-12.
6. Burton B. Drug industry to fight New Zealand's move to ban direct to consumer advertising. *Br Med J* 2004;328:1036.
7. Mansfield PR, Mintzes B, Richards D, Toop L. Direct to consumer advertising. *Br Med J* 2005;330:5-6.
8. Drug advertising. Australian Consumers' Association. <http://www.choice.com.au/viewarticle/leasonepage.aspx?id=104325&catId=100231&tid=100008&p=1> [cited 2006 Mar 8]
9. Coney S. Direct-to-consumer advertising of prescription pharmaceuticals: a consumer perspective from New Zealand. *J Pub Policy Mark* 2002;21:213-23.
10. Description of the joint regulatory scheme for the advertising of therapeutic products. Australia New Zealand Therapeutic Products Authority. 2005. <http://www.tgamedsafe.org/advert/advmodel.htm> [cited 2006 Mar 8]

Further reading

- Galbally R. Review of drugs, poisons and controlled substances legislation. Final report Part A. Canberra: Therapeutic Goods Administration; 2001. <http://www.tga.gov.au/docs/html/rdpdf.htm> [cited 2006 Mar 8]
- United States General Accounting Office. Prescription drugs. FDA oversight of direct-to-consumer advertising has limitations. Washington, DC: GAO; 2002. <http://www.gao.gov/new.items/d03177.pdf> [cited 2006 Mar 8]
- The House of Commons Health Committee. The influence of the pharmaceutical industry. Fourth Report of Session 2004-05. London: The Committee; 2005. http://www.parliament.uk/parliamentary_committees/health_committee/health_committee_reports_and_publications.cfm [cited 2006 Mar 8]

Conflict of interest: none declared

Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Eplerenone

Editor, – I read with interest the new drug review of eplerenone (*Aust Prescr* 2005;28:130–1). This review contains a number of statements that require clarification.

First, it is stated that gynaecomastia and breast pain still occur with eplerenone (as has been a major adverse effect of spironolactone). This is a somewhat disingenuous interpretation of the data as in fact no study has shown an excess of these events with eplerenone compared to placebo. As with any adverse effect, there is a spontaneous background event rate that is not further added to by eplerenone therapy.

Next, it is implied that because spironolactone reduces relative risk of death by 30% in patients with severe heart

failure it is a more effective drug than eplerenone, that 'only' reduced risk of death by 15% in post-myocardial infarction (MI) heart failure patients. Again, making comparisons regarding the impact of therapies **across** trials is poor science and tells us nothing about the relative merits of individual drugs because of the differing disease states and background treatments in the differing trials.

Finally, and most importantly, it is stated that spironolactone is well known and inexpensive and 'thus unlikely to be superseded until more data about eplerenone are available'. This statement clearly implies that the two drugs can be used interchangeably for the same clinical indication. Just as eplerenone should not be given to patients with severe heart failure (because it has not as yet been tested in such a patient population) the same is true of spironolactone

in post-MI heart failure. The suggestion that these drugs are interchangeable challenges fundamental principles of evidence-based prescribing and should be utterly rejected.

Henry Krum
Professor and Director
NHMRC Centre of Clinical Research Excellence in
Therapeutics
Melbourne

Professor Krum has been a consultant to Pfizer, manufacturer of eplerenone.

Editorial comment:

Gynaecomastia may take several months to develop. While the frequency has not increased during studies of heart failure, it has been higher than with placebo in studies of hypertension. According to data reviewed by the US Food and Drug Administration 1% of men taking eplerenone for hypertension developed breast symptoms.¹

While the selectivity of eplerenone may explain why it has less effect on sex hormones than spironolactone, it is not clear if this results in greater efficacy. If the efficacy depends on aldosterone antagonism then spironolactone should also be effective. Spironolactone is known to be effective in heart failure, but, as Professor Krum highlights, the supporting evidence does not come specifically from patients who start treatment 3–14 days after an acute myocardial infarction. This has resulted in the cost-effectiveness of eplerenone being compared to placebo rather than spironolactone.²

As 50 patients need to be treated with eplerenone for a year to prevent one death, there is a need to find out if spironolactone could be more cost-effective. We would encourage a comparative trial of eplerenone and spironolactone, although there may be no incentive for the manufacturers to carry out this comparison.

References

1. US Food and Drug Administration. Clinical review: eplerenone. http://www.fda.gov/cder/foi/nda/2002/21-437_Inspra_Medr_P5.pdf [cited 2006 Mar 8]
2. Pharmaceutical Benefits Advisory Committee. Public summary document: eplerenone. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-eplerenone> [cited 2006 Mar 8]

Balsalazide sodium

Editor, –The New drug comment about balsalazide sodium (Aust Prescr 2005;28:104–6) described the use of this product by citing two 1998 studies which compared it to mesalazine in double-blind trials with ulcerative colitis patients.^{1,2} I wish to bring to your attention that the conclusions of these studies are not generalisable to the mesalazine products available in Australia, since the mesalazine product used in these studies

(Asacol) is not marketed in this country. Asacol has a different coating from the mesalazine products marketed in Australia.

There are several mesalazine formulations available globally, which have different coatings and therefore different release mechanisms^{3,4,5} which may lead to different therapeutic efficacy. These different formulations are also supplied in different strengths. The only two oral formulations of mesalazine available in Australia are Salofalk and Mesasal which are delayed-release preparations of mesalazine coated with a resin that dissolves at a pH greater than six (the approximate pH of the ileum/colon). In contrast, Asacol consists of 400 mg of mesalazine destined for release in the terminal ileum or colon as its resin coating dissolves at a pH greater than seven.

Mesalazine products with different coatings are not therapeutically equivalent and are not interchangeable. The results of the Abacus Investigator Group studies therefore cannot be generalised to all mesalazine preparations, including the oral preparations available in Australia. Such generalisations would be misleading.

The comment also claims that 'mesalazine is absorbed, but is rapidly metabolised and excreted in the urine'. However, like balsalazide, very little mesalazine is systemically absorbed after being orally administered. The active drug is believed to act topically on the intestine and the main route of elimination is the faeces.⁶

Tim Bownas
Medical Affairs Associate
Orphan Australia Pty Ltd
Berwick, Vic.

References

1. Abacus Investigator Group. Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis. *Gastroenterology* 1998;114:15-22.
2. Abacus Investigator Group. Maintenance of remission of ulcerative colitis: a comparison between balsalazide 3 g daily and mesalazine 1.2 g daily over 12 months. *Aliment Pharmacol Ther* 1998;12:1207-16.
3. Tromm A, Griga T, May B. Oral mesalazine for the treatment of Crohn's disease: clinical efficacy with respect to pharmacokinetic properties. *Hepato-Gastroenterology* 1999;46:3124-35.
4. Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *The Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No: CD000543 DOI: 10.1002/14651858. CD000543.
5. Sutherland L, Roth D, Beck P, May G, Makiyama K. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *The Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No: CD000544. DOI 10.1002/14651858 CD000544.
6. Orphan. Salofalk tablets and granules. Product information.

Suicide and antidepressants in children

Editor, –The editorial 'Suicide and antidepressants in children' (Aust Prescr 2005;28:110–11) is potentially misleading. It stated that there was a 'small but significant increase in suicide risk'. This is not so.

Analysis of the UK General Practice Research Database found no suicides among the 6976 people aged 10–19 years who had been prescribed one of two selective serotonin reuptake inhibitors (SSRIs) or two tricyclic antidepressants between 1993 and 1999; however, 15 people in that age group who died by suicide had not received an antidepressant.¹

Similarly, a toxicological review of 14 857 suicides between 1992 and 2000 in Sweden detected no SSRIs in the 52 suicides under 15 years of age. In the 15–19 years age group those taking SSRIs had a lower relative risk of dying by suicide than those taking other antidepressants.²

Clinicians with responsibility for children and adolescents can be reassured by these data, and by the American Academy of Child and Adolescent Psychiatry and the American Psychiatric Association guidelines³ which have been endorsed by over a dozen United States organisations comprising a 'national coalition of concerned parents, providers, and professional associations'. Similar guidance has been provided by the Australian/Australasian Colleges of General Practitioners, Physicians and Psychiatrists.⁴

In view of the strong association between child and adolescent mood disorders and suicide⁵, it does not appear prudent to withhold antidepressant medication in young people with severe depression if non-pharmacological measures are ineffective.

Robert D. Goldney

Professor of Psychiatry, University of Adelaide
Adelaide

References

1. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA* 2004;292:338-43.
2. Isacson G, Holmgren P, Ahlner J. Selective serotonin reuptake inhibitor antidepressants and the risk of suicide: a controlled forensic database study of 14,857 suicides. *Acta Psychiatr Scand* 2005;111:286-90.
3. American Psychiatric Association and American Academy of Child and Adolescent Psychiatry. The use of medication in treating childhood and adolescent depression: information for patients and families. <http://www.parentsmedguide.org/parentsmedguide.htm> [cited 2006 Mar 8]
4. Royal Australian and New Zealand College of Psychiatrists, Royal Australian College of General Practitioners, Royal Australasian College of Physicians. Clinical guidance on the use of antidepressant medications in children and adolescents. <http://www.racgp.org.au/downloads/pdf/20050509antidepressantguidelines.pdf> [cited 2006 Mar 8]
5. Shaffer D, Gould MS, Fisher P, Trautman P, Moreau D, Kleinman M, et al. Psychiatric diagnosis in child and adolescent suicide. *Arch Gen Psychiatry* 1996;53:339-48.

Professor Goldney has received honoraria and research grants from a number of pharmaceutical companies for presentations and research on depression.

Dr Jon N. Jureidini and Professor Anne L. Tonkin, authors of the article, comment:

Analysis by the US Food and Drug Administration (FDA) shows a statistically significant doubling (from 2 to 4%) in suicidal thinking and acts in randomised controlled trials. It is true that increased suicidal thinking and acts need not lead to completed suicide, but Professor Goldney seems unduly reassured by the fact that none of the 4000 individuals in those trials completed suicide. Based on 2003 Australian figures of 1.2 completed suicides/100 000 in people under 18 years old¹, a cohort 100 times greater is required to expect to see a single completed suicide in the time frame of these trials. While Professor Goldney is reassured by apparently favourable associations between antidepressant use and completed suicide, the data are inconclusive.²

In appealing to authority, Professor Goldney prefers the American Psychiatric Association and Academy of Child and Adolescent Psychiatry to the findings of US and British regulatory authorities cited in our paper. Inaccurate claims made by these organisations include 'a large number of clinical research trials ... have clearly demonstrated the effectiveness' of antidepressant medications for children and adolescents with depression.³ It seems that these organisations are subject to wishful thinking that things cannot be as bad for antidepressants as the evidence suggests.⁴ Further, unlike Professor Goldney, the report of the various professional colleges⁵ does not provide information about potential conflicts of interest.

General practitioners who find non-pharmacological means ineffective should be consulting with colleagues expert in child and adolescent mental health rather than prescribing unproven, potentially dangerous drugs.

References

1. Australian Bureau of Statistics. Canberra: ABS; 2005.
2. De Leo D, Evans R. International suicide rates and prevention strategies. Washington, DC: Hogrefe & Huber; 2004.
3. American Psychiatric Association and American Academy of Child and Adolescent Psychiatry. The use of medication in treating childhood and adolescent depression: information for patients and families. <http://www.parentsmedguide.org/parentsmedguide.htm> [cited 2006 Mar 8]
4. Tonkin A, Jureidini J. Wishful thinking: antidepressant drugs in childhood depression. *Br J Psychiatry* 2005;187:304-5.

5. Royal Australian and New Zealand College of Psychiatrists, Royal Australian College of General Practitioners, Royal Australasian College of Physicians. Clinical guidance on the use of antidepressant medications in children and adolescents. <http://www.racgp.org.au/downloads/pdf/20050509antidepressantguidelines.pdf> [cited 2006 Mar 8]

Thyroxine stability and formulation: why the secrecy?

Editor, – In May 2004 Australian pharmacists were instructed that thyroxine tablets should be stored refrigerated, before and after dispensing. This uniquely Australian directive, which carried the imprimatur of Sigma, the sole supplier of thyroxine tablets in Australia, and the Therapeutic Goods Administration, appears to have been ill-considered.¹ Dampness should be avoided during storage of thyroxine²; repeated daily opening of a refrigerated glass bottle over many months can make the tablets damp, with loss of potency.¹ Sigma has now conceded that tablets in current use from unsealed bottles should not be refrigerated¹, although pharmacists generally are unaware of this change. In letters to doctors and pharmacists during 2005, Sigma foreshadowed a change in formulation so that thyroxine tablets will be presented in five bottles of 40 tablets, with a recommendation to refrigerate the unopened bottles, but not the bottle in current use. In support of this change, Sigma refers to 'new stability data'. However, Sigma has refused to present these data for professional scrutiny, except under terms of a confidentiality agreement that precludes discussion or peer review.

The reasons for seeking public disclosure of these 'new stability data' have been set out in detail.³ The health of about 200 000 Australians depends on thyroid hormone replacement. They, and those who accept responsibility for prescribing this medication, have a right to know the details of the sole preparation that is available. If storage temperature is a key factor in maximising the tenuous shelf-life of thyroxine, our local data might be important in addressing the broader problems of stability, potency and bioavailability of thyroxine.^{4,5}

If we cannot achieve a culture of open disclosure between the pharmaceutical industry and consumers for a medication as straightforward as thyroxine, what chance do we have with medications that are shrouded in commercial confidentiality, contentious trial data, patent law and unexpected or contentious adverse effects? Do we really care whether there is an ethos of evidence-based medicine in the manufacturing, regulatory and dispensing arms of pharmaceutical practice? If so, the 'new stability data' should be made known. Only in that way can consumers establish whether the modified formulation is necessary, or whether it is being introduced as a face-saving initiative.

Jim Stockigt
Consultant Endocrinologist, Epworth and Alfred Hospitals
Professor of Medicine, Monash University
Melbourne

References

1. Stockigt JR. Should thyroxine tablets be refrigerated? Have we got it wrong in Australia? (with reply by Siddiqui O, Sigma Pharmaceuticals). *Med J Aust* 2005;182:650. http://www.mja.com.au/public/issues/182_12_200605/letters_200605-1.html [cited 2006 Mar 8]
2. Roberts GW. Taking care of thyroxine. *Aust Prescr* 2004;27:75-6.
3. The Endocrine Society of Australia. Issues of thyroxine stability and storage: current status.
4. American Association of Clinical Endocrinologists (AACE), The Endocrine Society (TES), and American Thyroid Association (ATA). Joint position statement on the use and interchangeability of thyroxine products. American Thyroid Association; 2004.
5. Stockigt J. Testing the bioavailability of oral L-thyroxine by studying its absorption: smoke or mirrors? *Thyroid* 2004;14:167-8.

The international influence of *Australian Prescriber*

Editor, – I enjoyed reading the commemorative issue of *Australian Prescriber* (*Australian Prescriber* – the first 30 years, *Aust Prescr* 2005;28:120–2). I did not know of the 'near death' or even the year the journal disappeared. It just goes to show the struggle we have in trying to provide unbiased drug information in the face of enormous biased commercial interest.

One important fact missing from the article was the role of *Australian Prescriber* in the Asia-Pacific region. We in drug regulation and as teachers of clinical pharmacology in medical schools really appreciate copies of *Australian Prescriber*. The articles are avidly read by medical students (especially when prompted that examination questions may be based on them) and even by drug regulators in the region. For example, when evaluating a new chemical entity submitted for registration, reviews of the drug evaluation by *Australian Prescriber* are included in the dossier and provide a very important supportive tool for the regulators.

I would therefore like to add the congratulations of many people in the region to the *Australian Prescriber* on its 30 years. We hope that the journal will continue to be an independent source of information for our region for many more years.

Krisantha Weerasuriya
Regional Adviser, Essential Drugs and Other Medicines
World Health Organization South-East Asia Regional Office
New Delhi
India