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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Adverse reactions to complementary medicines
- ☆ Avoiding fetal abnormalities with isotretinoin
- ☆ Bisphosphonates and osteonecrosis of the jaw
- ☆ Statins contraindicated in pregnancy

Please report **all** suspected reactions to these **Drugs of Current Interest**

Aripiprazole (Abilify)
Atomoxetine (Strattera)
Ezetimibe (Ezetrol)
Fenofibrate (Lipidil)
Iron sucrose (Venofer)
Levetiracetam (Keppra)
Pimecrolimus (Elidel)
Reboxetine (Edronax)
Sibutramine (Reductil)

1. ADVERSE REACTIONS TO COMPLEMENTARY MEDICINES

There is a widespread belief in the public that complementary medicines are safe, because they are 'natural'. A recent South Australian survey found that 52% of adults had used at least one complementary medicine the previous year, and 57% had not told their doctor about their use of these products.[1] Complementary medicine products have not been subjected to the pre-registration evaluation of efficacy and adverse effects required for pharmaceuticals. Since there is a lack of systematic data, together with a perception of safety and frequent non-disclosure of use to medical practitioners, there may be unrecognised adverse effects occurring with complementary medicines.

In Australia, the term 'complementary medicine' includes many herbal products, vitamins, minerals, amino acids and essential oils. Most complementary medicines are regulated by the TGA[2] to ensure that they conform with lists of permitted ingredients, and are manufactured under the same standards as pharmaceuticals.

Australian legislation exempts from these regulatory controls medicines, including complementary medicines, that are dispensed or extemporaneously formulated for the treatment of a particular individual. This means that complementary healthcare practitioners may dispense medicines containing certain herbal ingredients not assessed or regulated by the TGA. Unregulated complementary medicines, including those obtained through the Internet, may be contaminated with pharmaceutical substances, such as NSAIDs or steroids, or with toxic heavy metals such as lead, mercury or arsenic.[3]

Some complementary medicines have well-recognised adverse effects (see Table). These effects may be either predictable, as in the case of overdoses from the caffeine in guarana,[4] or idiosyncratic, such as allergic reactions to *Echinacea*.[5] Some reactions with complementary medicines may be serious or life-threatening. Two recent Australian cases have been published of liver failure requiring transplantation with black cohosh (*Cimicifuga racemosa*).[6,7] Although the association has not been established, ADRAC now has seven reports of hepatic reactions with this herb.

Complementary medicines may also interact with prescription medicines, for example St John's wort may lead to reduction in plasma concentrations of a number of medicines, including cyclosporin and oral contraceptives, and may cause serotonin syndrome when used with SSRIs or tramadol.[8] A large number of herbs, including garlic (*Allium sativum)*, Korean ginseng (*Panax ginseng*), and *Ginkgo biloba* have documented interactions with warfarin,[8] and there is some evidence that glucosamine and cranberry juice (*Vaccinium* species)[9] might increase the activity of warfarin as well.

Table: Selected adverse reactions of some complementary medicines

Complementary medicine	**Adverse reaction**
Aristolochia species*	Renal failure
Bee products	Anaphylaxis
Black cohosh *(Cimicifuga racemosa)*	Liver impairment
Echinacea species	Allergic reactions
Ginkgo biloba	Interaction with warfarin → bleeding
Guarana (*Paullinia cupana*)	Caffeine overdose
St John's wort *(Hypericum perforatum)*	Reduced efficacy of cyclosporin, oral contraceptives; Serotonin syndrome with SSRIs, tramadol

* Not a permitted ingredient in Australia

Health professionals are advised to question patients about their use of complementary medicines, and if an adverse reaction or an interaction involving a complementary medicine is suspected, to report it to ADRAC using any of the normal methods. All complementary medicines regulated by the TGA will have on the label an AUSTL or AUSTR code (L for listed; R for registered). Please include this code when making a report to ADRAC, as it is the best way to identify the exact product involved.

References

1. MacLennan AH, et al. *Preventive Medicine* 2002;35:166-173.
2. McEwen J. *Aust Prescriber* 2004;27:156-8.
3. Saper RB, et al. *JAMA* 2004;292:2868-73.
4. Problems with caffeine. *Aust Adv Drug Reactions Bull* 2000;19:3.
5. Allergic reactions with Echinacea. *Aust Adv Drug Reactions Bull* 1999;18:3.
6. Whiting PW, et al. *Med J Aust* 2002;177:440-1.
7. Lontos S, et al. *Med J Aust* 2003;179:390-1.
8. Fugh-Berman A. *Lancet* 2000;355:134-8.
9. Suvarna R, et al. *BMJ* 2003;327:1454.

2. AVOIDING FETAL ABNORMALITIES WITH ISOTRETINOIN

Isotretinoin (Accure, Oratane, Roaccutane) is a well-known major human teratogen, absolutely contraindicated in pregnancy. It is essential that it is not taken at any stage of pregnancy. Birth defects documented with isotretinoin include CNS malformations, eye abnormalities, absence or malformation of the ears, cardiac defects, cleft palate, and thymus and parathyroid abnormalities.[1] Of 115 pregnancies prospectively reported to the manufacturer, 18% ended in spontaneous abortion and 23% resulted in a live born infant with at least one malformation.[2] Further, 52% of isotretinoin-exposed 5 year olds were of subnormal intelligence.[3]

ADRAC has received two reports of isotretinoin-related fetal abnormalities associated with early first trimester exposure. In one case, multiple congenital abnormalities included double outlet left ventricle and deafness, and in the other, the baby had developmental delay and micropinna.

Of 73 additional ADRAC reports of fetal exposure to isotretinoin, one ended in spontaneous abortion, one was stillborn at 30 weeks and the others were listed either as termination of pregnancy, planning termination or outcome unknown. In three cases the patient had stopped using contraception while continuing isotretinoin. In one case the patient became pregnant with an IUCD in situ and in a further case the patient had an initial negative pregnancy test then commenced isotretinoin prior to having her next period (which didn't occur because she was pregnant).

In Australia prescribing of isotretinoin is restricted to dermatologists and specialist physicians, but in some states there is also limited provision for authorisation of prescribing by general practitioners. Also, in addition to statements in the product information and consumer medicine information, the packaging (carton) for the product has the following warning: "Causes birth defects. Do not use if pregnant. Do not become pregnant during use or within 1 month of stopping treatment." Prescriptions can be for up to 60 capsules with three repeats. This means that patients may continue to take isotretinoin without frequent medical review.

The Australian scheduling of isotretinoin requires that before a woman commences therapy, the prescriber must "ensure that the possibility of pregnancy has been excluded."[4] It is also required that women are advised to avoid becoming pregnant during isotretinoin treatment and for 1 month after completion of therapy.[4] Women should receive counselling on contraception and effective contraception should be commenced no less than a month before beginning treatment.

References
1. Roaccutane Product Information, Roche Products Pty Ltd, Australia, 19 Sep 2002.
2. Dai WS, et al. *J Am Acad Dermatol* 1992;26:599-606.
3. Adams J. *Teratology* 1990;41:614.
4. *Standard for the Uniform Scheduling of Drugs and Poisons* No.19, 2004, Appendix D2.

3. BISPHOSPHONATES AND OSTEONECROSIS OF THE JAW

A serious and disabling complication of bisphosphonate treatment, osteonecrosis of the jaw, has been described in a total of 99 cases in two large case series.[1,2] To date, ADRAC has received nine such reports.

Most of the cases have occurred following intravenous pamidronate (Aredia, Pamisol) and/or zoledronate (Zometa) therapy for malignancy, but several have occurred after oral treatment with alendronate (Fosamax) or risedronate (Actonel) for osteoporosis. Of the published cases, 82% followed dental surgery.[1,2] Presentation includes jaw pain, toothache, exposed bone and possibly also altered sensation and recurrent soft-tissue infection. The condition results in chronic pain and disfigurement and is resistant to treatment. Early diagnosis may reduce morbidity.

Prescribers are advised to have a dental review conducted of patients scheduled to receive intravenous bisphosphonates, so that dental procedures can be completed prior to commencement of therapy.[3] Patients and their dentists should be advised of the risk of osteonecrosis of the jaw so that any 'toothache' developing during treatment can be fully assessed for cause before treatment of the tooth commences.

References
1. Marx RE. *J Oral Maxillofac Surgery* 2003;61:1115-7.
2. Ruggiero SL, et al. *J Oral Maxillofac Surgery* 2004;62:527-34.
3. Greenberg MS. *Oral Surg Oral Med Oral Pathology Oral Radiology & Endodontology* 2004;98:259-60.

4. STATINS CONTRAINDICATED IN PREGNANCY

The Australian Drug Evaluation Committee (ADEC) has recently changed the pregnancy classification of the statins (atorvastatin, Lipitor; fluvastatin, Lescol, Vastin; pravastatin, Pravachol; simvastatin, Lipex, Simvar, Zocor) from category C to category D (see box). The statins were already contraindicated in pregnancy and the change follows publication of a series of cases of fetal malformation including effects on the central nervous system and limb abnormalities associated with first trimester exposure to a statin.[1] Cholesterol and other steroids are essential to fetal development including the formation of cell membranes, and the adverse effects of statin exposure during pregnancy may not be reversible. Women contemplating pregnancy should not be taking a statin, and women becoming pregnant while taking a statin should discontinue it immediately.

> Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Reference
1. Edison RJ, Muenke M. *New Engl J Med* 2004;350:1579-82.

WHAT TO REPORT? (you do not need to be certain, just suspicious!)

ADRAC encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, OTC medicines, herbal, traditional or alternative remedies. ADRAC particularly requests reports of:

*ALL suspected reactions to NEW DRUGS (see **DRUGS OF CURRENT INTEREST,** front page**)**
*ALL suspected drug interactions
*Suspected reactions causing
- •Death
- •Admission to hospital or prolongation of hospitalisation
- •Increased investigations or treatment
- •Birth defects

For blue cards
Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from the front of the "Schedule of Pharmaceutical Benefits" and the "Australian Medicines Handbook", from the Adverse Drug Reactions Unit ☎ 02-6232-8386, or from the website: http://www.tga.gov.au/adr/bluecard.pdf

Reports can also be submitted electronically, by going to the TGA web site (http://www.tga.gov.au) and clicking on "report problems" on the left.

For further information from the ADRAC Secretariat:

☎ 1800 044 114 Fax: 02-6232-8392 Email: adrac@health.gov.au

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The Bulletin is also available on the Internet at: http://www.tga.gov.au/adr/aadrb.htm (with full references)

All correspondence to be addressed to: The Secretary, ADRAC, PO Box 100, Woden, ACT, 2606