

Prepared by the Adverse Drug Reactions Advisory Committee (ADRAC) and the Adverse Drug Reactions Unit (ADRU) of the TGA. Members of ADRAC are: Associate Professor Duncan Topliss (Chair), Dr Michael Gold, Dr Vicki Kotsirilos, Associate Professor Cecilie Lander, Professor John McNeil, Associate Professor Peter Pillans, Associate Professor Simone Strasser, Dr Dana Wainwright

AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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

Atomoxetine (Strattera)
Ezetimibe/Simvastatin (Vytorin)
Fenofibrate (Lipidil)
Iron sucrose (Venofer)
Lumiracoxib (Prexige)
Moxonidine (Physiotens)

Pregabalin (Lyrica)
Rosuvastatin (Crestor / Viacor)
Strontium ranelate (Protos)
Teriparatide (Fortéo)
Ziprasidone (Zeldox)

1. Clozapine and myocarditis

Clozapine, marketed in Australia since 1993, is an effective antipsychotic for the management of treatment-resistant schizophrenia. All patients taking clozapine are enrolled in a registry and monitored regularly, primarily to detect the development of neutropenia and agranulocytosis.

A range of cardiac disorders has been associated with the use of clozapine, the most serious being myocarditis and cardiomyopathy. A boxed warning alerting prescribers to these reactions is included in the Product Information for clozapine.

A recent article reviewed 116 cases of suspected myocarditis associated with the use of clozapine that had been reported to ADRAC during 1993-2003.¹ In these 116 reports, 78% of patients were male and median age was 30 (range 16-61 years); this compares with 67% males and median age 37 (range not stated) for patients enrolled in one of the Australian clozapine registries.

Twelve of the ADRAC reports (10%) described a fatal outcome; however in 38% of reports the outcome was either unknown or "not yet recovered" at the time of reporting.

Over the period 1993 to 2003, ADRAC received 2782 reports of suspected adverse reactions associated with clozapine use, including 90

reports of cardiomyopathy and 57 reports of NMS. The most commonly-reported reactions were neutropenia (457 reports), pyrexia (276), and tachycardia (259).

Clozapine-associated myocarditis generally develops early after starting treatment, often within the first 28 days (median 17 days in the reports to ADRAC). The initial symptoms may be non-specific, such as tachycardia, fever, and flu-like symptoms. These initial symptoms can overlap considerably with those of other cardiac and non-cardiac conditions, including neuroleptic malignant syndrome (NMS), which may itself be caused by antipsychotics.

Prescribers should be aware that potentially fatal myocarditis may develop early after the commencement of clozapine. Patients who develop persistent tachycardia, arrhythmias, shortness of breath or other signs of heart failure, or unexplained fatigue, chest pain or fever, should be evaluated urgently for the presence of myocarditis. Strong consideration should be given to ceasing clozapine while suspicious symptoms and signs are evaluated. If myocarditis is confirmed, clozapine should be discontinued.

Reference:

1. Haas SJ, Hill R, Krum H *et al.* Clozapine-associated myocarditis. *Drug Safety* 2007; 30: 47-57.

2. Mirtazapine and blood dyscrasias

Mirtazapine, an antidepressant, is an analogue of mianserin and, like mianserin, has been associated with reports of neutropenia and agranulocytosis.

Since 2001 when the drug was registered, blood dyscrasias in association with mirtazapine have been reported to ADRAC in 36 patients (21 males and 15 females, age range 29 to 94 years). These include 5 reports of agranulocytosis and a further 19 of neutropenia. The Committee has also received 7 reports of severe pancytopenia and 6 of thrombocytopenia. In 21 of the 36 reports, mirtazapine was the sole suspected drug. Median time to onset was 3 weeks (range 3 days to 6 months).

Two reports described fatal outcomes, one from pneumonia associated with neutropenia and another from haemorrhage due to

thrombocytopenia. Recovery was documented in 19 cases, 11 had not recovered and the outcome remained unknown for the others at the time of reporting.

The Product Information for mirtazapine includes a special warning/precaution regarding the possibility of neutropenia and agranulocytosis and recommends that mirtazapine should be stopped and blood counts taken if the patient experiences symptoms such as fever, sore throat, stomatitis or other signs of infection.

On starting mirtazapine, patients should be warned of this rare but potentially life-threatening adverse reaction, informed of the symptoms of febrile neutropenia, and advised to report to their doctor promptly if symptoms develop.

3. Black cohosh and liver toxicity – an update

The herb *Cimicifuga racemosa* (black cohosh) is used predominantly for relieving the symptoms of menopause. The Bulletin first advised of an association between the use of products containing black cohosh and hepatotoxicity in April 2006.¹ The TGA website advised of new labelling and consumer information for products containing black cohosh in February 2006.²

Up to the end of 2006, ADRAC had received 16 reports where an association between black cohosh and hepatotoxicity was suspected. Eleven were considered likely to be causally related to black cohosh and one was considered to be certainly related because of a recurrence of the reaction upon re-challenge.

Three of the patients with suspected black cohosh-induced hepatotoxicity underwent liver transplantation.

In the first case, the patient presented with jaundice one week after commencing a product containing black cohosh.³ Other causes of liver failure were excluded.

In the second case the patient was admitted to hospital with liver failure.⁴ She had been taking Nurofen 200 mg intermittently over 1 month and a herbal tonic containing black cohosh, ground ivy, golden seal, oats and ginkgo biloba for approximately 2 months, ceasing 1 month prior to development of jaundice. She reported dark urine prior to taking Nurofen. Her liver biopsy showed massive necrosis. Black cohosh was considered the most likely cause of the hepatic failure although other substances (particularly the ground ivy) may have contributed.

In the third case a woman experienced weakness and tiredness for approximately 2 months.⁵ She had been taking a product containing black cohosh for approximately 3 years but no other medications apart from multivitamins.

Her black cohosh dose was doubled 2 weeks after her initial symptoms of weakness and tiredness developed. An abdominal ultrasound 6 days after the dose increase was suggestive of hepatitis. The pathology on liver biopsy was consistent with drug-induced liver injury.

There have also been 2 published cases outside Australia describing hepatic failure requiring liver transplantation following the use of black cohosh.^{5,6}

The TGA recently convened an Expert Advisory Group to undertake a critical review of the scientific literature relating to the safety and efficacy of black cohosh. The Group concluded that, on the basis of available evidence, there appears to be a very rare association between the consumption of black cohosh and liver toxicity.

As a result of the recent review, further changes to the labelling of products containing black cohosh are to be implemented to better inform consumers of this risk associated with the use of black cohosh.

Drug-induced liver injury should be suspected in all cases without a clear cause of abnormal liver enzymes. A full review of all medicines that a patient has been taking, including complementary medicines, is essential.

References:

1. ADRAC. Hepatotoxicity with black cohosh. *Aust Adv Drug React Bull* 2006; 25: 6
2. <http://www.tga.gov.au/cm/0705blkcohosh.htm>
3. Whiting P, Clouston A, Kerlin P. Black cohosh and other herbal remedies associated with acute hepatitis. *MJA* 2002; 177: 440-443.
4. Lontos S, Jones R, Angus P, Gow P. Acute liver failure associated with the use of herbal preparations containing black cohosh. *MJA* 2003; 179: 390-391.
5. Lynch CR, Folkers ME, Hutson WR. Fulminant hepatic failure associated with the use of black cohosh: a case report. *Liver Transplantation* 2006; 12: 989-992.
6. Levitsky J, Alli T, Wisecarver J, Sorrell M. Fulminant liver failure associated with the use of black cohosh. *Digestive Diseases and Sciences* 2005; 50: 538-539.

4. ADRAC celebrates 300 Meetings

The Australian Adverse Drug Reactions Advisory Committee was established in 1970 to provide independent advice to the TGA on matters relating to the safety of medicines. ADRAC first met on May 26 1970 and celebrated its 300th Meeting on May 11 2007. Over that time, ADRAC has overseen the review of over 220,000 reports and has provided a wealth of information and knowledge regarding matters of drug safety, thanks to the diligence, expertise and commitment of its Members.

Right: Dr Patrick Purcell (ADRU), Dr Ian Boyd (ADRU), Prof John McNeil, Dr Vicki Kotsirilos, Dr Michael Gold, A/Prof Cecile Lander, Dr Richard Hill (ADRU), Seated: Dr Dana Wainwright, A/Prof Duncan Topliss (Chair), A/Prof Simone Strasser (A/Prof Peter Pillans (inset) was absent)



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", or from the Adverse Drug Reactions Unit ☎ 02-6232-8744, 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>

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