Prepared by the Adverse Drug Reactions Advisory Committee (ADRAC) and the Adverse Drug Reactions Unit 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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- ☆ Traditional Indian (Ayurvedic) and Chinese medicines associated with heavy metal poisoning
- ☆ Zolpidem and bizarre sleep related effects
- ☆ Increased risk of fractures associated with enzyme-inducing antiepileptic medicines

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)
Teriparatide (Fortéo)

1. Traditional Indian (Ayurvedic) and Chinese Medicines associated with heavy metal poisoning

ADRAC has received a report of a married couple who both showed elevated blood lead levels after taking Ayurvedic herbal medicines, dispensed from an Indian hospital. The male, who had taken the unidentified Ayurvedic medicine for five months was admitted to a hospital in Australia with abdominal pain, nausea and vomiting secondary to lead poisoning. He had a lead level of 120 µg/dL and also high levels of arsenic and mercury. His wife was asymptomatic but also had a high lead level of 40 µg/dL. An acceptable blood concentration for lead is < 10 µg/dL.[1]

The TGA has released a statement about the safety of Ayurvedic medicines in Australia, in response to recent research into the toxic content of heavy metals found in some Ayurvedic medicines.[2]

There are several possible explanations for the presence of heavy metals in traditional herbal remedies.[3] Salts of heavy metals (for example those of lead, mercury and arsenic) are used as principal ingredients in some traditional Indian and (to a lesser extent) Chinese herbal remedies.[4] In addition, cross-contamination of ingredients can occur between these types of products and products not intended to contain metal salts if manufacturing conditions are not controlled.

The possibility of contamination and adulteration should be considered for any herb or herbal medicine purchased overseas, imported into Australia for personal use or obtained over the internet. Traditional Indian and Chinese medicines authorised for supply in Australia are regulated as 'complementary medicines' and are required by the TGA to meet set standards of manufacturing and quality that aim to ensure that medicines do not contain unsafe levels of these metals. These products can be identified by an AUST L number on the product label. No assurance can be provided about the standards of manufacturing or the content of heavy metals in herbal remedies or medicines that are not approved for supply in Australia.

If an illness occurs, the possibility of it being related to complementary medicines, conventional medicines, or both, should be considered. If an adverse reaction involving a herbal remedy or complementary medicine is reported to ADRAC, please provide information on where the medicine was obtained and (if available) include the AUST L number in the report as it is the best way to identify the exact product involved.

References:
1. http://www.cs.nsw.gov.au/csls/handbook/FactSheetView.asp?Number=25
2. Safety of Ayurvedic medicine in Australia. www.tga.gov.au/cm/ayurvedic.htm
3. Ernst E. Contamination of herbal medicines. *The Pharmaceutical Journal* 2005; 275; 167
4. Pharmacopoeia of the People's Republic of China. Beijing, China: People's Medical Publishing House 2005.

2. Zolpidem and bizarre sleep related effects

Zolpidem (Stilnox) was marketed in Australia in late 2000 for the short term treatment of insomnia. It is structurally unrelated to the benzodiazepines, but has a similar pharmacological action. In 2002, ADRAC reviewed the first year of use and it was noted about 75% of the reports received described one or more neurological or psychiatric reactions, especially visual hallucinations, confusion, depression and amnesia.[1] This pattern, which is not shared by other hypnotics, has continued with hallucinations (104 reports) and amnesia (62) now the most frequently reported effects. Reactions associated with sleeping or falling asleep have been described in half of all reports submitted. Of particular interest have been 16 reports of sleep walking, which describe inappropriate or strange automatic behaviour "while asleep", including binge eating and house painting.

There have been isolated reports in the literature describing sleep walking, including an article in the popular magazine *Time* which mentioned the impending publication of a case series describing a few dozen people who, after taking zolpidem,

developed uncontrollable urges to eat while asleep and did not remember the feeding binges when they awoke.[2] A case series describing 5 patients taking zolpidem who experienced uncontrolled eating while asleep has previously been published.[3] There are two reports to ADRAC that describe this situation. In one report, a patient put on 23 kg in weight over 7 months while taking zolpidem. It was only when she was discovered eating in front of an open refrigerator while asleep that the problem was resolved. In another report, a patient who had experienced significant weight gain was found by a relative taking food from the refrigerator and kitchen cupboards while asleep. Other reports to ADRAC describe a patient who woke with a paintbrush in her hand after painting the front door while asleep, a patient who walked around the house like a "mad man" while asleep, and two further reports which suggest the possibility of driving while asleep.

ADRAC recommends prescribers should be alert to the fact that zolpidem may be associated with distressing neurological or psychiatric reactions, including those associated with sleeping or falling asleep, and should warn their patients about the possibility of these untoward effects, particularly if they are going to take zolpidem for the first time.

References:
1. ADRAC. Seeing things with Zolpidem. *Aust Adv Drug React Bull* 2002; 21: 3.
2. Gorman C. Sleeping-pill puzzler. *Time* 2006, May 19.
3. Morgenthaler TI, Silber MH. Amnestic sleep-related eating disorder association with zolpidem. *Sleep Medicine* 2002; 3: 323-327.

3. Increased risk of fractures associated with enzyme-inducing antiepileptic medicines

Reduced bone mineral density and subsequent increased risk of fractures is documented in patients taking enzyme-inducing antiepileptic medicines such as phenytoin, phenobarbitone, and primidone long-term.[1] The risk is higher in women and increases with duration of exposure. Patients with epilepsy may have many reasons for increased fracture risk, eg. seizures, lack of exposure to sunlight and reduced mobility. Abnormalities of bone metabolism are seen with increased frequency in people taking antiepileptic medications. Biochemical abnormalities include: hypocalcemia, hypophosphatemia, reduced serum levels of biologically active vitamin D metabolites, and hyperparathyroidism. Bone turnover is also accelerated.[1]

Medicines which induce cytochrome-P450 enzymes are thought to increase the metabolism of vitamin D3, thus leading to vitamin D deficiency or insufficiency and a reduction in bone mineral density. A recent case control study noted a statistically significant reduction in bone mineral density in women aged over 40 years taking enzyme-inducing antiepileptic medicines for at least 2 years, but it was a small study and could not distinguish between the effects of individual antiepileptic medicines.[2]

At present there is no information regarding the effect of "new" antiepileptic medicines on bone health but this has not been examined in appropriate studies. Data may be confounded because of co-administration with older antiepileptic medicines.

ADRAC has received relatively few reports of reduced bone mineral density in association with antiepileptic medicines. This may reflect a low level of awareness of this important adverse effect and the delayed nature of the events, often occurring years after commencement of medication.

Patients taking antiepileptic medicines long-term should be advised to have safe but adequate sun exposure, perform weight-bearing exercise and avoid other risk factors for reduced bone mineral density such as alcohol and smoking. In some cases periodic monitoring of bone mineral density may be appropriate and use of supplemental calcium and vitamin D should be considered.

References:
1. Pack AM, Morrell MJ. Epilepsy and bone health in adults. *Epilepsy & Behaviour* 2004; 5(2); S24-S29.
2. Petty, SJ *et al*. Effect of antiepileptic medication on bone mineral measures. *Neurology* 2005; 65:1358-1365.

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