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# AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Nefazodone ? looks like an SSRI, but .....  
..... Hepatic dysfunction  
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- ☆ Viagra is here!

Prepared by the ADVERSE DRUG REACTIONS ADVISORY COMMITTEE  
(ADRAC), a subcommittee of the Australian Drug Evaluation Committee.

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Dr Dana Wainwright, Professor Lindon Wing.

## 1. NEFAZODONE ? LOOKS LIKE AN SSRI, BUT .....

Nefazodone (Serzone) is one of the new antidepressants which was marketed in Australia in mid 1997. It is related to the SSRIs but has a dual action in that it works on both sides of the serotonin synapse. It blocks the 5HT<sub>2</sub>-receptor and inhibits serotonin reuptake. It also has weak  $\alpha_1$ -adrenergic blocking activity. ADRAC has received 147 reports in association with nefazodone and the most commonly reported reactions are shown in the table.

### ..... HEPATIC DYSFUNCTION

Of particular importance are the reports of hepatic dysfunction. These developed from 3 weeks to a number of months after the drug was started. In the 8 reports in which liver function tests were provided, significant rises in alanine amino transferase (ALT) to between 473 and 3380 U/L (reference range: 0-40 U/L) and in aspartate amino transferase (AST) to between 176 and 1326 U/L (reference range: 0-40 U/L) were noted. Three patients presented with jaundice. In one of these, a liver biopsy was consistent

### ..... VISUAL DISORDERS

The reports of visual disturbance highlight some unusual effects. While five of them described blurred vision, and two others described mydriasis, the others described such curious effects as “visual lag”, “thought my glasses were scratched”, “light more visible and shadows and textures compelling”, “cobwebs in front of the eyes” (two reports described this effect), “triple vision”, “shimmering in the periphery”, “trail of images”, “flashing lights with tails”, “multiple images”, “stripe in the visual field”,

## 2. ONDANSETRON AND CHEST PAIN

Ondansetron (Zofran) is a 5HT<sub>3</sub>-receptor antagonist which is indicated for the prevention and treatment of nausea and vomiting induced either by cytotoxic therapy or radiotherapy, or occurring postoperatively. Since its marketing in 1991, ADRAC has received a total of 232 reports in association with the drug. Of these, 19 have described chest pain, including myocardial ischaemia (1 report) and/or myocardial infarction (2 reports) in association with ondansetron. In the 5 cases described below, the drug was given in a situation unrelated to, or not simultaneously with, chemotherapy.

Most Commonly Reported Reactions with Nefazodone	
Nausea/Vomiting	24
Abnormal Vision	20
Dizziness/Vertigo	14
Headache	14
Fatigue	10
Somnolence	10
Ataxia	10
Confusion	10
Hepatic Dysfunction	10
Tremor	9
Anxiety	7

with drug-induced hepatitis. At the time the reports were submitted, 4 patients had recovered, 2 had not recovered, and 3 were improving. The other patient, who was taking nefazodone, trifluoperazine and oxazepam developed jaundice, encephalopathy and hepatic failure and died during a liver transplant operation.

and “after image when turns head from side to side only at night”. There was also a report of greatly decreased visual acuity.

There is limited postmarketing experience with nefazodone and prescribers should be aware that in these two respects, at least, nefazodone appears to have some differences in its adverse reaction profile compared to established SSRIs.



In one report, a 48 year old female developed dysaesthesia, numbness, headache, nausea, left upper limb pain and chest tightness 20-30 minutes after the second ondansetron injection. A third injection the following day produced similar, but more severe symptoms. In another case, a 62 year old female was given intravenous ondansetron for nausea due to migraine and she experienced angina-like chest pain associated with ECG changes. In a third case, two weeks after maintenance chemotherapy, a 20 year old female was administered intravenous ondansetron and within a minute of starting the infusion, she developed

central chest pain, shortness of breath and a dry cough. The symptoms resolved on stopping the infusion but they recurred when the infusion was restarted. In two other cases in which ondansetron was the only suspected drug, chest pain was associated with the use of two oral doses given to control nausea and vomiting in one report, and in the other, chest tightness occurred after intravenous ondansetron.

In the other 14 cases, ondansetron was administered concurrently with chemotherapy so it is possible that one of the cytotoxic drugs was the cause of the chest pain. However, the use of ondansetron was a common link. Apart from one patient who developed a fatal myocardial infarction in association with a paclitaxel (Taxol) protocol, all the patients recovered.

There have also been literature reports of this association. In one report, 7 cases were documented and in another report, the reaction recurred on rechallenge with ondansetron.<sup>1,2</sup> The reports to ADRAC suggest that chest pain is a possible adverse effect of ondansetron. As the drug becomes more widely used in the treatment of post-operative and other causes of nausea and vomiting, this effect may become more apparent.

#### References:

1. Ballard HS, Bottino G, Bottino J. Ondansetron and chest pain. *Lancet* 1992; 340: 1107.
2. Frigerio C, Buchwalder PA, Spertini F. Ondansetron: reasons to be restrictive. *Lancet* 1996; 347: 1484-5.



### 3. VIAGRA IS HERE!

Nitrates and VIAGRA must not be used concomitantly (see CONTRAINDICATIONS).

VIAGRA is contraindicated in men for whom sexual intercourse is inadvisable due to cardiovascular risk factors (see CONTRAINDICATIONS and precautions).

As most readers would be aware, sildenafil citrate (Viagra) was recently marketed in Australia for the treatment of erectile dysfunction in adult males. It carries the above boxed warning.

In the United States, where the drug has been marketed since late March, 69 patients have died after using Viagra. In the 48 patients in whom the cause of death was known, 2 had strokes and 46 had cardiovascular events. The average age of the men involved was 64 years and 12 men also took a nitrate, which is contraindicated. Fifty one of the 69 patients had one or more risk factors for cardiovascular events and 3 additional persons had coronary artery disease detected at autopsy.

In Australia, there has been one report involving the drug. It is poorly documented but describes a man who died after using the drug.

The relatively large number of reports of death is difficult to interpret as the drug is used in a group of patients with significant risk factors for cardiovascular events. Erectile dysfunction may have been caused by cardiovascular disease and sexual activity itself is a

further risk factor. However, there has been a recent report from The Netherlands in which a 65 year old man without a history of cardiovascular disease had an acute myocardial infarction within an hour of taking the drug but without engaging in sexual activity.<sup>1</sup>

Viagra has vasodilator properties and results in transient decreases in blood pressure that may unmask or aggravate ischaemic symptoms in men with cardiovascular disease. This effect may be potentiated by administration of nitrates. In the event that a patient taking Viagra develops a cardiac ischaemic event, the time of the last dose of Viagra should be established and nitrates should be avoided for the following 24 hours. Additional adverse effects identified in clinical trials included headache, flushing, and nasal congestion, all of which are related to vasodilatation. Other reported adverse effects were dyspepsia, abnormal vision and diarrhoea.

#### Reference:

1. Feenstra J, van Drie-Pierik RJHM, Laclé CF, Stricker BHCh. Acute myocardial infarction associated with sildenafil. *Lancet* 1998; 352: 957-8.



## WHAT TO REPORT?

The Adverse Drug Reactions Advisory Committee (ADRAC) encourages the reporting of all **suspected** adverse reactions to drugs and other medicinal substances, including herbal, traditional or alternative remedies. The reporting of seemingly insignificant or common adverse reactions may highlight a widespread prescribing problem. The Committee particularly requests reports of:


\*ALL suspected reactions to NEW DRUGS, especially **DRUGS OF CURRENT INTEREST**

\*ALL suspected drug interactions

\*Reactions to other drugs which are suspected of significantly affecting a patient's management, including reactions suspected of causing


- Death
- Danger to life
- Admission to hospital
- Prolongation of hospitalisation
- Absence from productive activity
- Increased investigational or treatment costs
- Birth defects

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from the Adverse Drug Reactions Section

 02-62328386, 02-62328387, 02-62328388, or from the website: <http://www.health.gov.au/tga/adr.pdf>

Tear-out blue cards can also be found at the front of all recent editions of the "Schedule of Pharmaceutical Benefits", and at Appendix F of the "Australian Medicines Handbook".

Further information can be found from the medical and scientific staff in the ADRAC Secretariat:

Secretary:  02-62328381 Executive Secretary:  02-62328382

Fax: 02-62328392

(Problems with therapeutic devices should be reported on 1800-809361)

The Bulletin can also be found on the Internet at the TGA website: <http://www.health.gov.au/tga>

### Drugs of Current Interest

<b>Acarbose (Glucobay)</b>	<b>Alendronate (Fosamax)</b>
<b>Atorvastatin (Lipitor)</b>	<b>Carvedilol (Dilatrend, Kredex)</b>
<b>Citalopram (Cipramil)</b>	<b>Diclofenac/misoprostol (Arthrotec)</b>
<b>Dicloxacillin (Diclocil, Distaph)</b>	<b>Dolasetron (Anzemet)</b>
<b>Donepezil (Aricept)</b>	<b>Fexofenadine (Telfast)</b>
<b>Fluvoxamine (Luvox)</b>	<b>Irbesartan (Avapro, Karvea)</b>
<b>Losartan potassium (Cozaar)</b>	<b>Nefazodone (Serzone)</b>
<b>Nicorandil (Ikorel)</b>	<b>Olanzapine (Zyprexa)</b>
<b>Sildenafil (Viagra)</b>	<b>Tiagabine (Gabitril)</b>
<b>Tiludronate (Skelid)</b>	<b>Topiramate (Topamax)</b>
<b>Zolmitriptan (Zomig)</b>	

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