



AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Bruising and bleeding with SSRIs
- ☆ Worldwide withdrawal of mibefradil
- ☆ Drugs that make you forget
- ☆ Depression with isotretinoin

Prepared by the ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC), a subcommittee of the Australian Drug Evaluation Committee. ADRAC is Dr Tim Mathew (Chair), Dr Paul Desmond, Dr David Isaacs, Dr Cecilie Lander, Professor Gillian Shenfield, Dr Dana Wainwright, Professor Lindon Wing.

1. BRUISING AND BLEEDING WITH SSRIs

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Erocap, Lovan, Prozac, Zactin), paroxetine (Aropax) and sertraline (Zoloft) have become widely used in Australia. Over the past few years their use in the treatment of depression and other disorders has increased considerably and ADRAC has been able to develop a comprehensive adverse effect profile. One effect which has emerged is **bruising** and **bleeding**, which in the majority of cases is not associated with thrombocytopenia but with platelet dysfunction. The numbers of reports of purpura/bruising, thrombocytopenia, bleeding and platelet dysfunction with these three SSRIs are shown in Table 1.

	Fluoxetine	Paroxetine	Sertraline
Total Reports	919	1036	2023
Purpura/ Bruising	20	38	16
Bleeding	10	16	41
Thrombo- cytopenia	9	10	5
Platelet dysfunction	5	5	4

* more than one reaction may be present in a report

The most common bleeding site was vaginal (24 cases) and other more commonly reported bleeding episodes were epistaxis (19), haematuria (10) and rectal haemorrhage (8).

Purpura appears to be an important adverse effect for the SSRIs. With 38 reports submitted to ADRAC, paroxetine is one of the most commonly reported causes of purpura. Only seven of these cases occurred in the context of thrombocytopenia.

Of the 14 reports documenting platelet abnormalities, 11 occurred in association with purpura or bleeding. Five of the reports documented abnormal platelet aggregation which is consistent with the postulate that fluoxetine may diminish granular storage of serotonin in platelets, creating a haemostatic defect which disrupts the platelet aggregation process, resulting in bleeding.^{1,2,3} It has been suggested that this is probably a rare situation which only occurs in individuals with an underlying platelet disorder or an altered platelet serotonin reuptake system.^{2,3}

References:

1. Alderman CP, Moritz CK, Ben-Tovim DI. Abnormal platelet aggregation associated with fluoxetine therapy. *Ann Pharmacother* 1992; 26: 1517-19.
2. Humphries JE, Wheby MS, Vandenberg SR. Fluoxetine and the bleeding time. *Arch Pathol Lab Med* 1990; 114: 727-8.
3. Pai VB, Kelly MW. Bruising associated with the use of fluoxetine. *Ann Pharmacother* 1996; 30: 786-8.



2. WORLDWIDE WITHDRAWAL OF MIBEFRADIL

Mibefradil (Posicor) is the first of a new class of calcium antagonists which blocks both T and L type channels. In Australia it had been approved for treatment of hypertension and/or chronic stable angina pectoris. Early in June the drug's sponsor announced a worldwide withdrawal of the drug because of its interactions with many other drugs.

Up until this time, ADRAC had received 55 reports of suspected adverse reactions associated with mibefradil.

Bradycardia was the single most common reaction and accounted for almost half the reports. Three other reports documented **interactions** of mibefradil with other drugs. Two reports described rhabdomyolysis

with gross elevation of creatine kinase after mibefradil was added to long term simvastatin therapy and the other report of a suspected interaction involved a 36 year old man whose cyclosporin level became elevated after mibefradil was added to his other therapy.

At the time of the withdrawal, more than 25 drugs were suspected of interacting with mibefradil. It was considered by the sponsor that this number and diversity of drugs could not be practically addressed by standard warning labels. Included in the potentially interacting drugs are amiodarone, astemizole, cisapride, cyclosporin, erythromycin, quinidine, simvastatin and terfenadine.



3. DRUGS THAT MAKE YOU FORGET

An elderly man taking allopurinol, diclofenac and gemfibrozil was prescribed simvastatin to help control his hypercholesterolaemia. After a couple of weeks he noticed a loss of memory for recent events. This problem resolved within two weeks of stopping simvastatin and recurred within a week of restarting the drug. In another report, a middle aged woman took an indomethacin capsule for back pain and developed amnesia for the 3 hour period prior to the ingestion of the capsule and for two hours afterwards. She then recalled that she had experienced a similar effect (which she did not associate with the drug at the time) two years previously after she had taken an indomethacin capsule.

Amnesia or memory impairment in association with drug therapy is a rare occurrence and of the 73,000 reports received by ADRAC over the past ten years, this adverse reaction is documented in only 219. There are some drugs such as the benzodiazepines which are established as a cause of amnesia which would not normally be the subject of a report to ADRAC because of the well-known association. Table 2 lists those drugs most commonly reported to ADRAC in association with this effect over the past 10 years. The table also lists the reports of amnesia as a percentage of the total number of reports for each drug. Since amnesia occurs in about 0.25% of the reports in the database, the reaction might be important for those drugs in which it occurs at a considerably higher percentage than 0.25%.

Of the 219 reports of drug-induced amnesia analysed,

Drug	Reports of Amnesia	Percentage of Total Reports for the Drug
Sertraline	19	0.9
Simvastatin	14	0.8
Paroxetine	8	0.8
Midazolam	5	2.1
Dothiepin	5	1.6
Moclobemide	5	1.0
Fluoxetine	5	0.5
Ranitidine	5	0.4

- The drug with the highest proportion of reports (7: 3.4%), dexfenfluramine, has recently been withdrawn.

there was a single drug suspected in the majority (84%) of the reports. Ages of the patients ranged from 5 to 98 (median: 48) years and the onset of the reaction varied from the day drug therapy was commenced to many years afterwards with most occurring during the first week of therapy. Over a quarter occurred on the day the drug was started. The reaction occurred on rechallenge in 16 of the reports and most of the patients had recovered at the time the report was submitted. A number of these cases were reminiscent of transient global amnesia suggesting that a drug cause should be considered in such instances.



4. DEPRESSION WITH ISOTRETINOIN

There has been recent publicity linking isotretinoin (Accure, Roaccutane) with depression. From 1985 to June 1998, ADRAC has received a total of 129 reports of suspected adverse reactions in association with isotretinoin. Of these, 12 have described **depression**. All the patients involved were young (age range: 15-40 years, median: 19 years, M:F = 9:3) and taking the drug for treatment of acne.

Two reports described the re-emergence of depression and in the other 10 reports, depression was noted for the first time. Two cases were described as severe and 4 cases had psychotic features. Three patients

developed suicidal thoughts and two patients attempted suicide. One of these had a fatal outcome. Of the other 11 patients, 3 had recovered after withdrawal of isotretinoin, one was improving with the use of an antidepressant, and the other 7 had not recovered at the time the report was submitted.

The product information for isotretinoin states that “depression has been reported in some patients on isotretinoin therapy” and ADRAC advises prescribers to be alert for any adverse mood changes in their patients taking isotretinoin and to withdraw the drug if these occur.





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

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

Acarbose (Glucobay)	Alendronate (Fosamax)
Atorvastatin (Lipitor)	Carvedilol (Dilatrend, Kredex)
Citalopram (Cipramil)	Diclofenac/misoprostol (Arthrotec)
Dicloxacillin (Diclocil, Distaph)	Dolasetron (Anzemet)
Fexofenadine (Telfast)	Fluvoxamine (Luvox)
Irbesartan (Avapro, Karvea)	Losartan potassium (Cozaar)
Nefazodone (Serzone)	Nicorandil (Ikorel)
Olanzapine (Zyprexa)	Tiagabine (Gabitril)
Topiramate (Topamax)	

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