

Prepared by the Adverse Drug Reactions Advisory Committee (ADRAC) and the Office of Medicines Safety Monitoring (OMSM) of the TGA. Members of ADRAC are: 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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- ☆ TGA approves H1N1 influenza virus vaccine
 - ☆ The long and the short of movement disorders with metoclopramide
 - ☆ Washout or taper when switching antidepressants
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Please report **all** suspected reactions to these **Drugs of Current Interest**

Duloxetine (Cymbalta)
Dabigatran (Pradaxa)
Paliperidone (Invega)
Pramipexole (Sifrol)
Ranibizumab (Lucentis)

Rivaroxaban (Xarelto)
Sitagliptin (Januvia)
Strontium ranelate (Protos)
Varenicline (Champix)

1. TGA approves H1N1 influenza virus vaccine

The Therapeutic Goods Administration (TGA) has approved the registration of Panvax H1N1 influenza vaccine, for use in adults and children 10 years of age and over.

At this stage, the TGA has not approved the vaccine for use in children less than 10 years of age, and is awaiting further data on the results of a paediatric clinical trial currently in progress.

Clinical trial data have demonstrated that Panvax is effective and well tolerated, with a side effect profile similar to that of seasonal flu vaccines. A single dose has been shown to provide an adequate immune response in most healthy adults. The manufacturing processes for the H1N1 vaccine are the same as for seasonal influenza vaccines.

Common short-lived side effects that occur with seasonal flu vaccines and may occur with Panvax

include soreness at the site of injection, headache, mild fever, body aches and fatigue for a short time after vaccination.

As with all medicines there is always the potential for unexpected or rare serious side effects to occur. In line with usual practice, the TGA, along with its expert advisory committees will be closely monitoring the side effects from the use of Panvax.

Healthcare practitioners are encouraged to report adverse reactions to Panvax H1N1 influenza vaccine by using the [online reporting form](#) available from the TGA website at <http://www.tga.gov.au> by telephoning 18 02 007, or using the [Blue Card](#) (see back page).

Information on the roll-out of the vaccine can be found at <<http://www.healthemergency.gov.au>>

2. The long and the short of movement disorders with metoclopramide

The selective D₂ dopamine receptor antagonist metoclopramide is a long-established antiemetic and antinauseant, available in several branded oral or injectable formulations (e.g. Anagrain, Maxolon, Metoclopramide Injection, Metomax, Pramin). Recently the US FDA required manufacturers of metoclopramide-containing products to strengthen warnings about the risks of its long term or high dose usage in the USA prescribing information.¹

It is timely to revisit the well documented extrapyramidal acute dystonic reactions and the less well-known occurrence of tardive dyskinesia.^{2,3,4}

Although acute dystonic-dyskinetic reactions are self limiting and rarely cause permanent damage, they are alarming and distressing and often require hospital admission. Acute dystonic reactions generally occur within 72 hours of exposure to metoclopramide and affect a younger demographic. We have received 111 reports of acute dystonic reactions associated with metoclopramide. The age range is predominantly from a few months, through childhood to young adults, with < 10% in those over the age of 40.

Tardive dyskinesia is a potentially more serious but less well known side effect of metoclopramide and presents as repetitive, involuntary movements

of the face, tongue or extremities. Symptoms are rarely reversible, even on withdrawal of metoclopramide and there is no known curative treatment. The risk of developing tardive dyskinesia with metoclopramide increases with age, female gender and duration of treatment/number of doses.

We have received 11 reports of tardive dyskinesia in association with metoclopramide-containing medicines, of which 9 occurred in women 68 years or older. Where details of time to onset from drug initiation were provided it was generally more than one year.

Prescribers are reminded of the risk for development of tardive dyskinesia in patients receiving long-term metoclopramide treatment, particularly in the elderly. All patients taking metoclopramide should be regularly reviewed to determine if continued treatment is necessary.

References:

1. FDA News release 26-2-09: FDA requires Boxed warning for metoclopramide-containing drugs.
2. Wiholm B-E, Mortimer O, Boethius G, Haggstrom J. Tardive dyskinesia associated with metoclopramide. *BMJ* 1984; 288: 545-547.
3. Product Information, metoclopramide/metoclopramide-containing products.
4. Bateman D, Rawlins M, Simpson J. Extrapyramidal reactions with metoclopramide. *BMJ* 1985; 291: 930-932.

3. Washout or taper when switching antidepressants

Antidepressants are indicated for the treatment of major depressive disorders and may be indicated also for anxiety disorders, obsessive compulsive disorder, premenstrual dysphoric disorder and/or chronic pain. They include:

Antidepressant class	Examples
Selective Serotonin Reuptake Inhibitors (SSRI)	Fluoxetine, citalopram, paroxetine, sertraline
Tricyclic antidepressant (TCA)	Nortriptyline, amitriptyline
Monoamine Oxidase Inhibitors (MAOI)	Phenelzine, moclobemide
Noradrenergic and 5HT1-serotonergic receptor agonist	Mirtazepine
Serotonin and noradrenaline reuptake inhibitors (SNRI)	Venlafaxine, duloxetine
Noradrenaline reuptake inhibitor	Reboxetine
Herbal	St John's Wort (<i>hypericum perforatum</i>)

These drugs have various mechanisms of action but they share a number of similar properties, which may predispose individuals to suffer from adverse effects due to interactions when switching antidepressants, even if they are of the same class.

One of the more serious possible outcomes is the development of serotonin syndrome – a potentially life threatening condition caused by the accumulation of serotonin in the central nervous system.¹⁻⁴

Serotonin syndrome is a potential adverse effect of all antidepressants not just SSRIs and it can occur when treatment is not interrupted as well as during switching, particularly in the elderly.^{1,3,4}

The risk of serotonin syndrome increases if there is simultaneous exposure to more than one drug that can cause this syndrome. We have received several reports describing this situation, some of which have described life-threatening outcomes.

To avoid the possibility of an interaction, an appropriate washout period is required to substantially clear the first antidepressant from the body before the second is introduced.

Unfortunately, no simple advice on the appropriate washout period can be given. In general, a drug is not completely cleared until a period equivalent to 4-5 half lives has elapsed after a drug is ceased.

The half life of antidepressants varies substantially from about 2 hours for citalopram and moclobemide up to 6 days or more for fluoxetine, while the effect of irreversible MAOIs such as phenelzine can persist for several weeks after the drug has been ceased.

Drug half life varies substantially amongst individuals and is often prolonged in the elderly or those with hepatic impairment or renal insufficiency. Pharmacokinetic and pharmacological interactions between drugs can also affect drug half life, which highlights the need to consider a washout or tapering period when switching between antidepressants.

There are no set guidelines on switching amongst antidepressants and factors that should be considered will vary depending on the properties of the antidepressants and the patient's situation including the duration of time the patient has been on the first antidepressant, patient age, other medications and other health issues.^{5,6}

If there are concerns about possible withdrawal syndrome, it may be more appropriate to taper the first drug before slowly introducing the second medicine to minimise the risk of withdrawal to the first as well as the risk of adverse reactions due to interactions when the second is introduced.^{5,6}

Useful information on antidepressant-free intervals when changing from one antidepressant to another is available in the Therapeutic Guidelines - Psychotropic medicines and in the Australian Medicines Handbook.^{5,6} This information as well as drug-specific information from product information documents for the drugs concerned should be consulted when switching antidepressants is considered.

References:

1. ADRAC. Serotonin syndrome. *Aust Adv Drug Reactions Bull* 2004; 23(1).
2. ADRAC. Tramadol and serotonin syndrome. *Aust Adv Drug Reactions Bull*. 2001; 20(4).
3. ADRAC. Serotonin syndrome with duloxetine. *Aust Adv Drug Reactions Bull*. 2009; 28(4).
4. Isbister G, Buckley N, Whyte I. Serotonin toxicity: A practical approach to diagnosis and treatment. *MJA* 2007; 187: 361-365.
5. Changing Antidepressants. *Australian Medicines Handbook* 2007, p 714.
6. Therapeutic Guidelines. Psychotropic. Version 6, 2008, pp 112-113.

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 website: <http://www.tga.gov.au/adr/bluecard.htm> or from the Office of Medicines Safety Monitoring ☎ 02-6232-8744.

Reports can also be submitted electronically, by going to the TGA website <http://www.tga.gov.au> and clicking on "report problems" on the left, by fax: 02-6232-8392, or email: ADR.Reports@tga.gov.au

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The Bulletin is also available on the Internet at: <http://www.tga.gov.au/adr/aadrb.htm>

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