

Prescriber Update

Vol. 25 No. 2
November 2004

From the Editor _____	16
COX-2 inhibitors – where to from here? _____	17
Clozapine patients presenting with symptoms of infection _____	18
Surveillance of adverse events following MeNZB™ immunisation _____	19
Diabetes and antipsychotic drugs _____	20
Potential for flu vaccine interactions exists _____	23
Updated information and advice about the use of antidepressant medicines (in children and adolescents) _____	25
Adverse Reactions of Current Concern _____	29
Medicines in the Intensive Medicines Monitoring Programme (IMMP) _____	30

A publication of



Prescriber Update is a
member of the



www.medsafe.govt.nz

Resources available to you on the Medsafe web site,
under the Health Professionals section:

- Data sheets
- Prescriber Update articles
- Medicine classification issues
- Adverse reactions reporting forms
- Consumer Medicine Information (CMI)

www.medsafe.govt.nz

FROM THE EDITOR

Use of POPs post-VTE

The Medicines Adverse Reactions Committee (MARC) recently reviewed its earlier July 2002 advice contraindicating the use of progestogen-only oral contraceptives (POPs) in women with current venous thromboembolism (VTE). The MARC has now realigned their advice to that provided by the World Health Organisation (WHO). Consequently, the MARC support the WHO recommendation that the use of a POP is not recommended in the presence of current VTE *unless other contraceptive methods are not available or are unacceptable.*

BNF available on-line: www.bnf.org

Full text access to the British National Formulary (BNF) is available at www.bnf.org for no charge. Registration is required and for this purpose, you will need to supply a valid e-mail address. Instructions for the registration process will be sent to that e-mail address. You can then complete registration by supplying your name, some details about the type of organisation you work in, and a password of your choosing. As a registered user you will have access to the full text of the current BNF for up to 15 minutes when you log on.

Travel medicine information: www.who.int/ith

International Travel and Health 2004 is a World Health Organisation publication about the health risks likely to be encountered in specific countries and associated with different types of travel. This guide provides information for medical professionals about the precautions needed to protect the health of travellers, such as recommended vaccinations and malaria prophylaxis. The 2004 edition is available on-line only (www.who.int/ith).

Updated HRT guideline summary and consumer leaflet available

In March this year, the New Zealand Guidelines Group (NZGG) published an updated summary on hormone replacement therapy (HRT). This can be obtained from the NZGG web site (www.nzgg.org.nz). There is also an HRT consumer leaflet available free from Wickliffe: phone 04 496 2277 – order no. HP3817. Alternatively, the leaflet can be printed from the NZGG web site.

Key to *Prescriber Update* articles

To assist readers in knowing the origin of articles published by Medsafe, the symbols below will appear next to the article title, where applicable.



Adverse Drug Reaction Update

articles are written in response to adverse reaction reports lodged with the Centre for Adverse Reactions Monitoring (CARM) and material in the international literature. These articles may also be written to alert prescribers and pharmacists to potential problems with medicines.



MARC Prescribing Advice articles are recommendations from the Medicines Adverse Reactions

Committee (MARC) in response to medicine safety issues and overseas experiences.

Medsafe Editorial Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in November 2004.

What happened and why?

On 1 October 2004, Merck Sharp & Dohme (MSD) announced their decision to withdraw Vioxx® (rofecoxib) worldwide due to concerns about its cardiovascular safety. These concerns arose from a three-year study (known as APPROVe*) undertaken to evaluate the efficacy of rofecoxib (25mg) versus placebo in preventing the recurrence of colorectal polyps. During this study, it was noted that the risk of cardiovascular adverse events such as myocardial infarction and cerebrovascular accidents was doubled in patients using rofecoxib for more than 18 months, compared to patients using placebo.

At the time of its withdrawal, Vioxx was approved for use in over 80 countries. It was registered in New Zealand in January 2000, and in the United States of America and United Kingdom in 1999. The risk of cardiovascular events was not detected in the pre-marketing clinical trials.

Why did the cardiovascular events occur?

There are a number of plausible mechanisms that may explain why rofecoxib appears to be associated with an increased risk of cardiovascular events. However, it is unclear which is more likely to be responsible. A prothrombotic or atherogenic effect may be involved.

What has Medsafe done?

From the date of first marketing, Medsafe (and other regulatory agencies around the world) have collected and analysed adverse reaction reports for rofecoxib and the other COX-2 inhibitors as part of standard post-marketing monitoring practice. In December 2000, both rofecoxib and celecoxib were added to the Intensive Medicines Monitoring Programme (IMMP); the reason being that these two medicines were the first in a new class of COX-2 specific anti-inflammatories.

In New Zealand, the Medicines Adverse Reactions Committee (MARC) had previously reviewed all significant data but found that the evidence for an association between any of the COX-2 inhibitors and increased cardiovascular events was inconclusive. The local pattern of use indicated that users of COX-2 inhibitors were older, had other co-morbidities and were often on multiple medicines that could have increased their risk of this type of event. Medsafe and MARC have also monitored and reviewed published literature on adverse events in general with the COX-2 inhibitors.

What is Medsafe doing now?

Medsafe will be asking MSD to supply full data on the APPROVe study, along with any other data not previously available. Sponsors of other COX-2 inhibitors will also be asked for updated safety data, including details of any studies underway. Medsafe will additionally be liaising with other regulatory authorities, such as the TGA (Australia), FDA (United States of America) and Health Canada (Canada). Published data on cardiovascular events for all the COX-2 inhibitors, along with New Zealand case reports of adverse reactions and any other available unpublished data, will be reviewed by the MARC. Advice will be provided to prescribers once analysis of all the evidence is completed.

What about the other COX-2 inhibitors?

At this stage, there is insufficient information available to comment on the cardiovascular safety of the other COX-2 inhibitors (i.e. celecoxib, etoricoxib, meloxicam, parecoxib and valdecoxib). Medsafe will be asking the MARC to determine whether the risk of cardiovascular events is similar for the other COX-2 inhibitors, in comparison to rofecoxib.

* Adenomatous Polyp Prevention on Vioxx

What should prescribers do?

As all stock of rofecoxib has been removed from New Zealand, prescribers will need to discuss alternative options with their patients. This requires consideration of both the adverse event profile of possible substitutes (such as NSAIDs or other COX-2 inhibitors) and patients' individual risk factors for gastrointestinal and cardiovascular harm. In some patients paracetamol may be an effective alternative.

Prescribers can assist in monitoring the safety of all COX-2 inhibitors by reporting adverse events to the Centre for Adverse Reactions Monitoring in Dunedin – see inside back cover for contact details and the reporting form.

Where to from here?

Once Medsafe has obtained all the necessary data and the MARC has completed its analysis, advice will be promulgated to prescribers. It is intended that this advice will take into account that issued

by other countries. In the interim, the following additional information is available:

- A copy of the Medsafe/Ministry of Health media statement (issued 1 October 2004) is on the Medsafe web site (www.medsafe.govt.nz).
- Information for consumers and health professionals, along with MSD's media statement, is available from the Vioxx web site (www.vioxx.com).
- The Australian National Prescribing Service has released a fact sheet on switching patients from Vioxx; this can be downloaded from their web site (www.nps.org.au/resources/content/nps_factsheet_vioxx_20041001.pdf).
- The *Australian Prescriber* journal has made available an advance publication of their article on the vascular effects of COX-2 selective inhibitors (www.australianprescriber.com/media_releases/2004/oct/vascular_effects_cox2.pdf).

CLOZAPINE PATIENTS PRESENTING WITH SYMPTOMS OF INFECTION



The antipsychotic clozapine (Clozaril[®], Clopine[®]) can cause potentially fatal neutropenia and agranulocytosis (number needed to harm = 59).¹

Patients on clozapine who present with evidence of infection such as flu-like symptoms, sore throat or fever should be investigated for a blood dyscrasia. This includes immediately arranging for a differential blood count, and making contact with the treating psychiatrist and mental health team. Depending on the blood test result and clinical situation, an urgent haematology referral or emergency hospital admission may be required.

Some antibiotics (e.g. sulphonamides, trimethoprim and erythromycin) may increase the risk of neutropenia when combined with clozapine, therefore concomitant use should be avoided.²

General practitioners should be aware of safety protocols established by the psychiatrist, including the essential requirement that patients on clozapine comply with regular blood tests (weekly during the first 18 weeks of therapy and at least every four weeks thereafter for the duration of clozapine treatment).

References

1. Wahlbeck K, Cheine M, Essali A, et al. Evidence of clozapine's effectiveness in schizophrenia: A systematic review and meta-analysis of randomized trials. *Am J Psychiatry* 1999;156:990-999.
2. Stockley I (ed.) *Stockley's Drug Interactions* (6th ed.) 2002: Pharmaceutical Press, London, p.717-718.

SURVEILLANCE OF ADVERSE EVENTS FOLLOWING MeNZB™ IMMUNISATION



Ministry of Health Meningococcal B Immunisation Programme

In the first two months of the roll-out of the Meningococcal B Immunisation Programme, from 19 July to 19 September 2004, more than 140,000 doses of MeNZB™ were administered. The Independent Safety Monitoring Board, established by the Health Research Council, has considered safety data for this period and advises that it has no particular issues of concern in relation to the safety of the MeNZB™ vaccine.

As of 24 September 2004, 88 reports of adverse events following MeNZB™ vaccination were reported to the Centre for Adverse Reactions Monitoring (CARM) in Dunedin. CARM notes that the number of reactions reported suggests that the rate of post-vaccination adverse events of clinical concern is low for MeNZB™. The most frequent individual reactions reported are listed in the following table.

Most frequent individual reactions reported to CARM following MeNZB™ vaccination

Reactions	Number of reports* received	Proportion of all reports received
Injection Site Reactions	26	30%
Rash	26	30%
Fever	21	24%
Vomiting	18	20%

* It should be noted that each report may include more than one reaction.

Whilst 30% of submitted reports identified localised reactions, systemic reactions (such as gastrointestinal events, fever, headache and musculoskeletal events) were reported in 44 (50%) of the reports. Six reports documented vasovagal/syncopal-type episodes, all of which occurred in teenage girls in the context of the school-based immunisation programme, and were subsequently categorised as anxiety-related injection reactions. No life threatening or unexpected events have been reported.

Health professionals are asked to continue reporting to CARM any health events following MeNZB™ immunisation that are unexpected, serious in nature or of clinical concern. See inside back cover for details on how and where to report to CARM.

Further information about the surveillance of MeNZB™ adverse events is available on the Ministry of Health web site: www.immunise.moh.govt.nz/documents/surveillanceofadverseevents.pdf

Other information about the Meningococcal B Immunisation Programme can be found at: www.immunise.moh.govt.nz

A copy of the MeNZB™ data sheet and Consumer Medicine Information (CMI) are available on the Medsafe web site: www.medsafe.govt.nz

DIABETES AND ANTIPSYCHOTIC DRUGS

Joseph Proietto, Sir Edward Dunlop Medical Research Foundation Professor of Medicine, University of Melbourne and Department of Medicine, Heidelberg Repatriation Hospital, Austin Health, Melbourne, Australia

Reprinted from *Australian Prescriber* 2004;27(5):118-119 with permission.

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in November 2004.

There is an increased risk of diabetes in patients with schizophrenia and this risk is elevated by some antipsychotic medications. The risk is greater with the atypical drugs clozapine and olanzapine and the low potency conventional antipsychotics than with risperidone or high potency conventional drugs. While weight gain may be a mechanism for the development of diabetes, a direct effect of these drugs on insulin action in muscle may also be an important contributor. Patients with major psychosis should be managed in the same way as other patients with diabetes, but difficulties in complying with diet, exercise and taking medication should be kept in mind. Treating cardiovascular risk factors is important.

Introduction

An impaired action of insulin (insulin resistance) in patients with schizophrenia was reported over 55 years ago and later confirmed in Australia.¹ The prevalence of diabetes in patients with schizophrenia was found to be higher than in the general population even before the widespread use of antipsychotic medication. The mechanisms underlying the relationship between schizophrenia and diabetes remain unknown.

Antipsychotic drugs and diabetes

It is now clear that some antipsychotic medications increase the risk of diabetes in patients with

schizophrenia. Rarely, this may present as diabetic ketoacidosis. The atypical medications (Table 1) have become widely used because of their lower rate of extrapyramidal adverse effects compared to older classes of medication such as the phenothiazines and the butyrophenones. However, while some of the atypical drugs are better tolerated, they also increase the incidence of diabetes. In patients younger than 40 years of age, the odds ratio for developing diabetes is 1.63 if they are taking an atypical antipsychotic.²

Table 1: Classification of antipsychotic medications available in Australia^a

Atypical	Low potency* conventional	High potency conventional
amisulpride	chlorpromazine	droperidol
aripiprazole	pericyazine	flupenthixol
clozapine	thioridazine	fluphenazine
olanzapine		haloperidol
quetiapine		trifluoperazine
risperidone		

* Low potency is defined as 'equivalent or less potent than chlorpromazine'.¹⁰

^a With the exception of aripiprazole, all the other antipsychotics are available in New Zealand

Not all antipsychotics increase the risk of diabetes to the same extent.³ In a survey of two large US health plans, the risk of developing diabetes over a year was found to be higher with olanzapine and ‘low potency’ conventional antipsychotics, but not with risperidone or ‘high potency’ conventional drugs (Table 2).⁴ In one prospective study 36.6% of patients treated with clozapine developed diabetes over a five-year period.⁵

Mechanism of antipsychotic-induced diabetes

The mechanisms responsible for the elevated risk of diabetes associated with some antipsychotics are not fully understood. It is known that the atypical antipsychotics and some of the low potency conventional antipsychotics cause weight gain⁶ and that, at least for olanzapine and clozapine, the magnitude of this weight gain correlates with the magnitude of the therapeutic

response.⁷ The weight gain in response to antipsychotic medication is also variable. Clozapine and olanzapine cause the greatest gain, risperidone and quetiapine moderate gain, and aripiprazole and amisulpride the least gain.⁸ However, at present insufficient information is available about some of the newer drugs to know what their weight gain and diabetogenic potential will prove to be with more widespread use.

Obesity can precipitate diabetes in susceptible people so weight gain is one mechanism for the increased incidence in diabetes. However, the fact that hyperglycaemia improves quickly after stopping the antipsychotic medication and that diabetes can appear in some patients who do not put on weight, suggests that other mechanisms must be involved. A prospective study of 82 patients treated with clozapine also found that the risk of developing diabetes was independent of weight gain.⁵

Table 2: Risk of developing diabetes with antipsychotic medication⁴

Drug	Number of patients	12-month odds ratio (95% CI)
Untreated	2644	1.0
Low potency conventional	302	4.972 (CI 1.967-12.612) [†]
High potency conventional	785	1.945 (CI 0.794-4.786)
Olanzapine	656	4.289 (CI 2.102-8.827) [†]
Risperidone	849	1.024 (CI 0.351-3.015)

CI confidence interval; [†] significant ($p < 0.05$) compared to untreated patients

Diabetes related to antipsychotic medication is associated with high insulin concentrations, so it seems that these drugs may aggravate the insulin resistance that already exists in patients with schizophrenia. While some of this is no doubt related to weight gain, it has also been shown that antipsychotics inhibit glucose transport into muscle. There is a strong correlation between the ability of these drugs to inhibit glucose transport *in vitro* and their capacity to induce hyperglycaemia *in vivo*.⁹

Management of diabetes in patients with schizophrenia

What needs to be taken into account when treating someone coping with the dual problems of schizophrenia and diabetes?

- Be alert to the increased risk of diabetes in patients with schizophrenia and the fact that some antipsychotic medications increase the risk. Check the patients’ fasting blood glucose and monitor their weight.
- Monitor blood glucose more frequently in patients with known diabetes who commence antipsychotic medication.
- Advise about diet and exercise, but keep in mind that compliance may be particularly difficult for patients with schizophrenia.
- When prescribing hypoglycaemic drugs, try to use once-daily medication so that treatment can be more easily supervised. While metformin (the preferred first-line therapy) should be given twice daily there are now two sulfonylureas that

are available as once daily medication (modified-release gliclazide and glimepiride^b).

- There is an increase in cardiovascular mortality in patients with schizophrenia so remember to regularly assess and vigorously treat cardiovascular risk factors such as dyslipidaemia and hypertension.
- In psychotic patients who have a family history of diabetes or in those who are from an ethnic group with a high prevalence of diabetes (all non-Europeans), try to use an antipsychotic that has less potential for precipitating diabetes, such as risperidone or one of the high potency conventional drugs (Table 2).

The management of diabetes in patients with a major psychiatric illness is problematic. Weight loss or prevention of weight gain should always be attempted because of the known benefits to other comorbidities associated with obesity. However, even if successful, this approach alone may not reduce the risk of developing or worsening diabetes.

Conflict of interest: none declared.

References

1. Martin FI, Alford FP. Insulin sensitivity in schizophrenia. *Br Med J* 1970;2:50.
2. Lean ME, Pajonk FG. Patients on atypical antipsychotic drugs: another high-risk group for type 2 diabetes: response to Hardy and Breier [letter]. *Diabetes Care* 2003;26:3202-3203.
3. Koro CE, Fedder DO, L'Italien GJ, et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *Br Med J* 2002;325:243.
4. Gianfrancesco F, Grogg A, Mahmoud R, et al. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. *Clin Ther* 2003;25:1150-1171.
5. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: A five-year naturalistic study. *Am J Psychiatry* 2000;157:975-981.
6. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry* 2001;62 Suppl 7: 22-31.
7. Czobor P, Volavka J, Sheitman B, et al. Antipsychotic-induced weight gain and therapeutic response: a differential association. *J Clin Psychopharmacol* 2002;22:244-251.
8. Clark NG. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004;27: 596-601.
9. Dwyer DS, Donohoe D. Induction of hyperglycemia in mice with atypical antipsychotic drugs that inhibit glucose uptake. *Pharmacol Biochem Behav* 2003;75:255-260.
10. Leucht S, Wahlbeck K, Hamann J, et al. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. *Lancet* 2003;361:1581-1589.

^b Neither glimepiride nor modified-release gliclazide are marketed in New Zealand

POTENTIAL FOR FLU VACCINE INTERACTIONS EXISTS



Medsafe Editorial Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in October 2004.

Prescribers are advised to be on the look out for signs of toxicity in patients taking anticonvulsants or warfarin who concurrently receive influenza vaccination.

Carbamazepine, warfarin and other medicines reported to interact with the influenza vaccine

In recent years, New Zealand public health campaigns to encourage prophylaxis with influenza vaccines (Fluarix™, Flu Vax™, Vaxigrip™) have targeted patient groups who are most at risk from influenza virus infection, such as people over 65 years of age or those with chronic diseases that impair infection response.¹ The target group include patients taking a number of medicines.

Reports of patients developing phenytoin, warfarin or theophylline toxicity following influenza vaccination have been published.²⁻⁵ In one study, toxic elevations in levels of the concurrent medicines were reported to occur up to 28 days post-vaccination.⁵

Other cases of possible interactions include:

- A report received by the Australian Adverse Drug Reactions Advisory Committee of a 45-year-old female patient on long-term carbamazepine therapy for epilepsy, who developed carbamazepine toxicity following the administration of an influenza vaccine; and
- A report received by Centre for Adverse Reactions Monitoring (CARM) of a 70-year-old female patient taking long-term warfarin. Within a week of receiving an influenza vaccine, her INR was noted to be significantly elevated.

No clear mechanism of action but hepatic enzymes may be involved

The mechanism of action for these interactions is suspected to involve cytochrome P450 3A4 hepatic enzyme inhibition, leading to reduced clearance of the concurrently administered medicine.* However, not all published cases support this explanation;⁴ for example, the interaction between warfarin and the influenza vaccine is thought to more likely involve an alteration in the synthesis of blood clotting factors.⁷

While increasing age may be a risk factor for enzyme inhibition by the influenza vaccine, overall, the potential for interaction has high inter-individual variability.⁸ The effectiveness of the influenza vaccine is not thought to be affected.

Prescribers and patients should be alert for signs of toxicity

In general, influenza vaccines are not associated with clinically significant interactions. However, these case reports highlight the possibility that the influenza vaccine may interact with some concurrent medicines, particularly those with a narrow therapeutic index.

Prescribers are asked to look for signs of toxicity with any of the medicines metabolised by cytochrome P450 3A4 in patients who are co-administered an influenza vaccine. Increased monitoring of anticoagulant therapy is recommended.

* Medicines affected by the cytochrome P450 3A4 enzyme include carbamazepine, warfarin, statins, phenytoin, ketoconazole, theophylline, cisapride, calcium-channel antagonists, protease inhibitors, benzodiazepines and some tricyclic antidepressants.⁶

Inform patients of signs of toxicity, particularly for anticonvulsants where frequent monitoring is not likely to be practical. In all instances, ask patients to report symptoms immediately to their doctor. If toxicity is suspected, check appropriate blood levels.

The possible risk of interactions should not preclude patients from being administered an influenza vaccine. Any suspected vaccine-medicine interactions should be reported to CARM in Dunedin (see inside back cover for details).

Competing interests (authors): none declared.

References

1. Ministry of Health. Recommended immunisation schedule. *Immunisation Handbook 2002*; Wellington, p.184. Available as a PDF on the Ministry of Health web site: www.moh.govt.nz
2. Poli D, Chiarugi L, Capanni M, et al. Need of more frequent International Normalized Ratio monitoring in elderly patients on long-term anticoagulant therapy after influenza vaccination. *Blood Coagul Fibrinolysis* 2002;13:297-300.
3. Robertson WC. Carbamazepine toxicity after influenza vaccination. *Pediatr Neurol* 2002;26:61-63.
4. Meredith CG, Christian CD, Johnson RF, et al. Effects of influenza virus vaccine on hepatic drug metabolism. *Clin Pharmacol Ther* 1985;37:396-401.
5. Jann MW, Fidone GS. Effect of influenza vaccine on serum anticonvulsant concentrations. *Clin Pharm* 1986;5:817-820.
6. Cupp MJ, Tracy TS. Cytochrome P450: New nomenclature and clinical implications. *Am Family Physician* 1998;57(1):107. www.aafp.org/afp/980101ap/cupp.html
7. Stockley IH (Ed). *Stockley's Drug Interactions* 6th edn. London: Pharmaceutical Press, 2002.
8. Hayney M, Buck J. Effect of age and degree of immune activation on cytochrome P450 3A4 after influenza immunization. *Pharmacotherapy* 2002;22:1235-1238.

UPDATED INFORMATION AND ADVICE ABOUT THE USE OF ANTIDEPRESSANT MEDICINES



The following letter was sent by Medsafe to all prescribers and pharmacies on 19 October 2004. It was also published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers.

19 October 2004

Dear Health Professional,

Re. Updated information and advice about the use of antidepressant medicines

The purpose of this letter is to update prescribers on the risks and benefits associated with the use of Selective Serotonin Reuptake Inhibitor (SSRI)* and Tricyclic Antidepressant (TCA)** medicines for treating Major Depressive Disorder (MDD). The Medicines Adverse Reactions Committee is issuing the following advice and information based on a review of current evidence:

- 1. SSRI risk/benefit in childhood and adolescent MDD** – For childhood and adolescent MDD, the possible risk of suicidal ideation and behaviours (suicidality) with SSRIs generally outweighs the possible benefits. However, there is some evidence of efficacy with fluoxetine and therefore it may have a favourable risk/benefit ratio. There is no evidence from clinical trials of an increased risk of *completed* suicide in any age group using SSRIs.
- 2. TCA risk/benefit in childhood and adolescent MDD** – For childhood and adolescent MDD, the risk/benefit ratio for TCAs is generally unfavourable because of the risk of cardiovascular toxicity and the lack of demonstrable efficacy in children (and only modest efficacy in adolescents).
- 3. Informed consent** – Use of SSRIs or TCAs in children and adolescents may be warranted in particular circumstances. In these cases, individual risk/benefit discussions between doctor and patient/parent must be undertaken and informed consent obtained.
- 4. Antidepressant risk/benefit in adult MDD** – For all antidepressants, the risk/benefit ratio in adult MDD remains favourable. Although there is some evidence that there may be an increased risk of suicidality in adults taking SSRIs, the overall proven efficacy of these medicines outweighs the possible risks.
- 5. Monitor all patients with depression** – All patients with MDD should be monitored for the emergence or worsening of suicidal thoughts and behaviours regardless of whether they are taking an antidepressant medicine or not.

Specialist advice should be sought before initiating, changing or stopping any antidepressant therapy in children and adolescents. Patients currently on an antidepressant who are responding well should complete the usual course of treatment. Antidepressant medicines should not be stopped abruptly – doses should be tapered off gradually. Where therapeutic response is inadequate specialist advice should be sought.

* SSRIs currently marketed in New Zealand are citalopram, escitalopram, fluoxetine, paroxetine, reboxetine and sertraline. Venlafaxine is a Selective Serotonin Noradrenaline Reuptake Inhibitor with similar properties to the SSRIs.

** TCAs currently marketed in New Zealand are amitriptyline, clomipramine, desipramine, doxepin, dothiepin, imipramine, nortriptyline and trimipramine.

On 22 March 2004, Medsafe sent a letter to prescribers regarding the use of Selective Serotonin Reuptake Inhibitors (SSRIs) in children and adolescents. The letter detailed some concerns that had arisen over the past year relating to possible lack of efficacy, and possible risk of suicidal ideation and behaviours, when these medicines are prescribed to treat children and adolescents with Major Depressive Disorder (MDD).¹ The Medicines Adverse Reactions Committee (MARC) has now considered further information regarding the use of SSRIs and Tricyclic Antidepressants (TCAs) in persons under 18 years of age, including recommendations from the US Food and Drug Administration (FDA) advisory committees,² the New Zealand branch of the Faculty of Child and Adolescent Psychiatry,³ and published medical literature.^{4,9}

SSRI risk/benefit in childhood and adolescent MDD

Risk – In September 2004, two FDA advisory committees discussed an analysis of paediatric suicidality data, based on new case classifications provided by Columbia University.² The FDA advisory committees concluded that there is some evidence of increased risk of suicidality associated with all SSRIs studied. The MARC is in broad agreement with this conclusion. In addition, the MARC still considers the data on SSRIs and suicidality to be inconclusive in establishing the *strength* of this association and it is unclear whether any one particular SSRI carries a greater risk of suicidality than others. There is no clinical trial evidence to associate SSRIs with risk of *completed* suicide in any age group.

Benefit – In previous reviews of SSRI clinical trials in children and adolescents by the UK Committee on Safety of Medicines (CSM) and the FDA, there appeared to be some evidence of efficacy for fluoxetine in MDD which is supported by a recently published large study in adolescents.⁴ There is no conclusive evidence of efficacy for any other SSRIs in childhood and adolescent MDD.

Risk/benefit ratio – For SSRIs, the possible risk of increased suicidality without any clinical trial evidence of efficacy in treating MDD results in SSRIs having a generally unfavourable risk/benefit ratio in treating childhood and adolescent MDD.

The one exception is fluoxetine, which appears to have a favourable risk/benefit ratio in children and adolescents. In some circumstances, the risk/benefit ratio of the other SSRIs may become more favourable when other factors are considered that may affect clinical management, such as treatment-resistant depression.

Other conditions – The use of specific SSRIs for other approved conditions in childhood and adolescence, such as obsessive-compulsive disorder, bulimia nervosa and premenstrual dysphoric disorder, should only be upon the advice of a specialist.

TCA risk/benefit in childhood and adolescent MDD

Risk – Published trials and reviews indicate that TCAs are consistently associated with increases in blood pressure, heart rate, and ECG abnormalities at normal therapeutic doses in children and adolescents. In this age group, there have been case reports of sudden cardiac death associated with TCA use. This is thought to be a very rare and possibly idiosyncratic event.^{5,6}

Benefit – A meta-analysis of trials examining TCA efficacy in MDD reveals that TCAs have no established efficacy in treating childhood MDD and only modest efficacy in treating adolescent MDD.⁷

Risk/benefit ratio – For TCAs, the risk of cardiovascular toxicity generally outweighs the possible therapeutic benefits in treating childhood and adolescent MDD. However, in adolescents the risk/benefit ratio may be favourable in some circumstances, particularly treatment-resistant depression. The New Zealand branch of the Faculty of Child and Adolescent Psychiatry consider that in such cases clinical management should be under the care of a Child and Adolescent Psychiatrist.³

Other conditions – A review of TCA use in the treatment of childhood enuresis identifies that the risk/benefit ratio is unfavourable and indicates TCAs generally no longer have a place in the treatment of this disorder.⁸ The use of specific TCAs for other approved indications in childhood and adolescence, such as obsessive-compulsive disorder and phobias, should only be upon the advice of a specialist.

Informed consent

In New Zealand, none of the SSRIs have ever been approved for use in treating MDD in children and adolescents. Some TCAs are currently approved for childhood and adolescent MDD. However, the MARC will request that the datasheets for TCAs be updated to state that these medicines are not recommended for use in patients under 18 years of age, unless upon the advice of an appropriate specialist. Essentially, this change will result in no class of antidepressant being approved for the treatment of MDD in children and adolescents.

The MARC recognises that the unapproved (or 'off-label') use of medicines is sometimes appropriate. In such instances, the Medicines Act 1981 allows a doctor to prescribe a medicine for any indication regardless of whether it is approved or not for that indication. There are limitations to this authority embedded in the Code of Health and Disability Services Consumers' Rights 1996. Unapproved use of medicines must comply with this Code, which states that the patient has the right to treatment of an appropriate ethical and professional standard, and the doctor has the responsibility to ensure that treatment, whether approved or unapproved, meets this standard. The patient also has the right to be fully informed. If the use of a medicine is unapproved, the patient should be so advised and the doctor should be frank about the level of evidence for the medicine's efficacy as well as any safety concerns. The doctor must fully discuss the risk/benefit issues with the patient/parent, and in appropriate circumstances this may lead to the use of an antidepressant with informed consent. (For more information on unapproved use of medicines see Medsafe article: www.medsafe.govt.nz/Profs/RIss/unapp.htm)

Antidepressant risk/benefit in adult MDD

The MARC considers that for all antidepressants the risk/benefit ratio in adult MDD remains favourable. Although there is some evidence that there may be an increased risk of suicidal ideation and behaviours in adults taking SSRIs, particularly those experiencing akathisia,¹⁰ the overall benefits outweigh the possible risks.¹¹

Monitor all patients with depression

The MARC considers that for all age groups worsening depression remains the most common reason for increased suicidality during treatment with any antidepressant. All patients with MDD should be monitored for the emergence or worsening of suicidal thoughts or behaviours regardless of whether they are taking an antidepressant medicine or not. Evidence suggests that the risk of suicidality may be especially increased during the first few weeks of treatment.⁹

Finally, the MARC considers that the possible increased risk of suicidality in patients applies to *all* classes of antidepressant medicines, as available data are not adequate to exclude an increased risk of suicidality for any antidepressant (including SSRIs, TCAs and Monoamine Oxidase Inhibitors). The Committee maintains a high priority on reviewing the safety of antidepressant medicines as more data become available.

signed by

Dr Stewart Jessamine

*Principal Technical Specialist
Medsafe*

References

1. Medsafe. Dear Health Professional [letter] – The use of SSRI antidepressants in children and adolescents. 22 March 2004. www.medsafe.govt.nz/hot/NZSSRIdoctorletter.pdf
2. FDA statement on Recommendations of the Psychopharmacologic Drugs and Pediatric Advisory Committees. www.fda.gov/bbs/topics/news/2004/NEW01116.html
3. Faculty of Child and Adolescent Psychiatry New Zealand Branch. Tricyclic antidepressants for treating Major Depressive Disorder in Children and Adolescents. *Personal Correspondence*. 16 September 2004.
4. March J, Silva S, Petrycki S, et al. Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *Journal of the American Medical Association* 2004;292(7):807-820.
5. Wilens TE, Biederman J, Baldessarini RJ, et al. Cardiovascular effects of therapeutic dose of tricyclic antidepressants in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry* 1996;35:1491-1501.
6. Varley C. Case Study: Sudden death of a child treated with Imipramine. *Journal of Child and Adolescent Psychopharmacology* 2000;10:321-325.
7. Hazell P, O'Connell D, Heathcote D, et al. Tricyclic drugs for depression in children and adolescents (Cochrane Review), [Online], Available: *OVID/Cochrane Database of Systematic Reviews* [26 Feb 2002].
8. Drug and Therapeutics Bulletin. Management of bedwetting in children. *Drug and Therapeutics Bulletin* 2004; 42(5):33-37.
9. Jick H, Kaye J, Jick S. Antidepressants and the risk of suicidal behaviors. *Journal of the American Medical Association* 2004;292:338-343.
10. Ellis P. Agitation, restlessness and suicidal behaviour with fluoxetine, paroxetine and sertraline. *Prescriber Update* 2002;23(3):37-38. www.medsafe.govt.nz/Profs/PUarticles/SSRI.htm
11. Geddes JR, Freemantle N, Mason J, et al. Selective serotonin reuptake inhibitors (SSRIs) versus other antidepressants for depression (Cochrane Review), [Online], Available: *OVID/Cochrane Database of Systematic Reviews* [29 Nov 2003].

ADVERSE REACTIONS OF CURRENT CONCERN



The Medicines Adverse Reactions Committee (MARC) initiated the list of *adverse reactions of current concern* to bring particular medicine adverse reactions to the attention of prescribers. The intention is to encourage prescribers to report these reactions to the Centre for Adverse Reactions Monitoring (CARM) so that more information can be gathered, and further action taken if necessary. The reports provide a New Zealand perspective on emerging medicine safety issues.

As with any adverse reactions monitoring scheme, analysis can only be based on reports that are received. Prescribers are therefore encouraged to continue reporting adverse reactions to CARM so that the MARC can make the best possible recommendations based on information reflecting the New Zealand situation.

Regular amendments to the list of reactions are made either in response to adverse events reported in New Zealand or international pharmacovigilance issues.

Please report **all cases** of the following adverse reactions to: CARM, NZ Pharmacovigilance Centre, PO Box 913, Dunedin. Use the reporting form inside the back cover of *Prescriber Update*, or download the form from the CARM or Medsafe web sites: www.otago.ac.nz/carm or www.medsafe.govt.nz/Profs/adverse.htm

Medicine/s	Adverse reactions of current concern	<i>Prescriber Update</i> reference
Complementary and alternative medicines*	all adverse reactions	Vol.23(2), July 2002 & No.13, Oct 1996
Leflunomide	all adverse reactions	Vol.25(1), May 2004
SSRI antidepressants	severe agitation, severe restlessness/akathisia, and/or increased suicidality	Vol.23(3), Nov 2002

* includes herbal medicines, bee products, homoeopathic products, dietary supplements, minerals, and any other medicines containing animal or plant extracts.

About the IMMP

The purpose of the Intensive Medicines Monitoring Programme (IMMP) is to identify previously unrecognised adverse reactions to new medicines. It also develops adverse reaction profiles for these medicines, as well as measuring incidence and characterising reactions of clinical concern. In addition, the IMMP is able to identify any high-risk groups amongst the patients being treated. The results of IMMP findings are used to enhance the safe use of medicines.

Which medicines are monitored?

Medicines of a new class may be added to the IMMP so that unknown adverse effects can be identified as soon as possible. Medicines may also be included in the programme if they are similar to other medicines for which safety concerns exist.

Medicines currently monitored by the IMMP

Medicine	Proprietary name/s
Celecoxib*	Celebrex
Clozapine	Clozaril, Clopine
Etoricoxib*	Arcoxia
Levonorgestrel intrauterine system*	Mirena
Olanzapine	Zyprexa
Quetiapine	Seroquel
Risperidone	Risperdal
Rofecoxib*	Vioxx
Sibutramine*	Reductil
Valdecoxib	Bextra

* New patients are no longer being added to the cohorts for these medicines because sufficient numbers of patients have already been recruited. However, follow-up of existing patients is continuing so adverse event data are still being collected for these medicines.

What to report

Please report **all clinical events** in patients taking IMMP medicines, including:

- any suspected adverse reaction
- deaths (including cause if known)
- any new clinical events, even if minor or common
- accidents
- change in a pre-existing condition
- abnormal changes in laboratory test results
- possible interactions.

Where to report

Please report all adverse events occurring with IMMP medicines to: IMMP, NZ Pharmacovigilance Centre, PO Box 913, Dunedin. Use the reporting form inside the back cover of *Prescriber Update*, or download the form from either the NZ Pharmacovigilance Centre or Medsafe web sites: www.otago.ac.nz/carm or www.medsafe.govt.nz/Profs/adverse.htm

What to tell patients prescribed IMMP medicines

Please remember to tell patients that they have been prescribed a monitored medicine. This means the IMMP receives details of their prescriptions and that their doctor may be asked for clinical information on the patient's experience whilst taking this medicine. If possible, an explanatory IMMP leaflet should be given to the patient (available from the IMMP, NZ Pharmacovigilance Centre, PO Box 913, Dunedin).

Prescriber Update is published and distributed by Medsafe in the interests of safer, more effective use of medicines, medical devices and methods of diagnosis and treatment.

Medsafe: New Zealand Medicines and Medical Devices Safety Authority
A business unit of the Ministry of Health.

Editor: Sarita Von Afehl
Medsafe, PO Box 5013, Wellington, New Zealand
Ph: (04) 496 2107 Fax: (04) 496 2229
E-mail: sarita_von_afehl@moh.govt.nz

Editorial Team: Dr Stewart Jessamine Principal Technical Specialist
Dr Sharon Sime Pharmacovigilance Advisor
Dr Jonathan Moy Medical Advisor

Manager, Medsafe: Clare Van der Lem

Medsafe web site: www.medsafe.govt.nz

*Published with the permission
of the Director-General of Health.*

Adverse reactions: What to report

Please report any suspect reaction of clinical concern. This includes adverse reactions involving:

- Prescription medicines
- Over-the-counter medicines (medicines purchased without a prescription)
- Complementary medicines (herbal medicines, naturopathic and/or homoeopathic medicines, and nutritional supplements such as vitamins and minerals)
- Vaccines.

In particular, please report the following:

- All suspected reactions to NEW medicines
- All events to IMMP medicines¹
- All Adverse Reactions of Current Concern²
- All suspected drug INTERACTIONS
- UNEXPECTED or SERIOUS reactions (including those suspected of causing death, admission to hospital, prolongation of hospitalisation, or birth defects)
- Serious ALLERGIC reactions (to enable a danger or warning to be entered in the national health database so re-exposure can be avoided for that individual).

How to report

Fill in the reporting form, which is available:

- overleaf (inside the back cover of *Prescriber Update*)
- from the CARM web site: <http://carm.otago.ac.nz/reporting.asp>

On-line reporting is also available on the CARM web site.

Where to report

Send all adverse reaction reports to CARM (Centre for Adverse Reactions Monitoring) in Dunedin.

Post to: Freepost 112002
 The Medical Assessor
 CARM
 NZ Pharmacovigilance Centre
 P O Box 913
 Dunedin

Fax: (03) 479 7150

Phone: (03) 479 7247

E-mail: carmnz@stonebow.otago.ac.nz

1. The list of medicines in the Intensive Medicines Monitoring Programme (IMMP) is on page 30

2. The list of *Adverse Reactions of Current Concern* is on page 29