

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/Rlss/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.



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References:

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