Suicidality with SSRIs: adults and children

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Suicidality with SSRIs: adults and children

In 2004, ADRAC published a statement on the use of SSRI antidepressants* in children and adolescents, in view of evidence that use of these agents in these age groups was associated with an increased risk of suicidality, including suicidal ideation, suicide attempts and self-harm events.1 SSRIs are not registered for the treatment of depression in those less than 18 years of age, and neither are any other antidepressants.

Recently, ADRAC conducted a review of the evidence of suicidal thoughts and behaviour associated with the use of SSRIs in adults. The Committee concluded that, in most adult patients, SSRIs in the treatment of depression are beneficial or cause no harm. However, it was noted that individual case reports, including some describing dechallenge and rechallenge, support an association between SSRI use and new onset suicidality.2,3 When this syndrome occurred it tended to develop soon after introduction of an SSRI, or an increase in the dose and to be associated with akathisia, agitation, nervousness and anxiety. The effect often persisted with continuing treatment. Similar symptoms can follow withdrawal of the SSRI.

Despite evidence of the infrequent occurrence of suicidal thoughts and behaviour with SSRIs, a recent large case control study by Jick et al found that prescription of fluoxetine or paroxetine, both SSRIs, was not associated with suicidal behaviour more frequently than prescription of the tricyclic antidepressant (TCA), dothiepin.4 Participants were all first-time users of antidepressants and individuals at high risk of suicidality were excluded.

The Jick study included 17 suicides, and these occurred much more frequently in the first 9 days after starting antidepressants than later in the treatment period. This increased risk of suicide early in therapy may occur because the antidepressant has not yet taken effect, because the medication was begun when the depression was at its worst, or because of an activation effect of the medication.

A meta-analysis of 702 randomised controlled trials found an association between treatment with an SSRI and suicide attempt when compared with placebo, but in common with the Jick study, when TCAs were the comparator no difference in frequency was found.5 There was no difference between SSRIs and placebo for fatal suicide attempts.

Increased prescribing of antidepressants in Australia during 1991-2000 was associated with decreasing suicide rates, with the trend being most apparent in older age groups.6 These results do not demonstrate a causal relationship, but the authors suggest the trend may be indicative of improved overall management of depression, including treatment at the primary care level, use of psychosocial intervention and prescribing of SSRIs (first available in the early 1990s). The SSRIs have brought many advantages, including once daily administration, lower rates of key adverse reactions, and safety in overdose.

Because of the risk of suicidal ideation and behaviour in both adults and children being treated for major depression and other psychiatric disorders, the TGA has recently required the sponsors of antidepressants, including the SSRIs, to update their Australian product information with appropriate warnings. The warnings provide the following advice:

- Worsening of depressive symptoms and emergence of suicidality may occur with treated or untreated depressive illness;
- Patients should be closely monitored for suicidality in the first weeks of treatment, and if there is a change in dose (up or down);
- Consideration should be given to changing or discontinuing therapy if worsening of symptoms persists or emergence of suicidality occurs with treatment;
- Patients and caregivers should be advised to monitor for worsening illness, suicidal or self-harm-related thoughts and behaviour and advised to seek medical assistance immediately should these occur.

* The SSRI antidepressants included are citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, and the related medicine, venlafaxine.

References
2. Ezetimibe and muscle disorders

Ezetimibe (Ezetrol) lowers lipids by inhibiting the intestinal absorption of cholesterol and is indicated for the treatment of hypercholesterolaemia. Out of 144 Australian reports received with ezetimibe since registration in June 2003, 44 have been of muscle disorders, including myalgia, muscle cramp, weakness and pain with five reports describing increased serum creatine kinase (CK) and three listing symptoms possibly indicative of an allergic reaction.

In premarketing clinical trials, reported rates of myalgia were less than 2% with ezetimibe, 2.4% with statins and 3.2% with ezetimibe coadministered with a statin.1 The association of the lipid-lowering statins (atorvastatin, fluvastatin, pravastatin, simvastatin) with muscle disorders, including rhabdomyolysis, is well-known.2 Although ezetimibe has been associated with muscle disorders, at present it is uncertain whether it can cause rhabdomyolysis, and if so what factors increase the risk.3

In the 44 cases reported to ADRAC with muscle disorders, the time to onset ranged from hours to approximately 4 months, but in almost half of the cases, the symptoms developed within two weeks. Twenty-one patients had a history of muscle disorder or increased CK with statins.

Ezetimibe was given concomitantly with a statin in 5 of the 44 cases and in two published cases.4 The details of these cases are consistent with an interaction between the statin and ezetimibe. Typically, the patient had been taking the statin long term, and the symptoms of myalgia or increase in creatine kinase developed within three months of the addition of ezetimibe. Four patients recovered on withdrawal of ezetimibe alone, and another tolerated reintroduction of atorvastatin 80mg daily without ezetimibe.

ADRAC encourages reporting of cases of muscle disorders with ezetimibe, especially cases which are serious or involve increased creatine kinase.

References

3. Pathological gambling with cabergoline

In the past 2 years ADRAC has received 4 reports describing the development of pathological gambling in association with cabergoline (Cabaser). These are the only 4 reports of this problem in the ADRAC database. All 4 patients were taking long-term levodopa and the excessive gambling commenced a number of months after cabergoline was added. In 3 of the 4 Australian cases, the patient also developed obsessive, inappropriate or abnormal behaviour. In all cases the gambling and other behavioural problems resolved when cabergoline was stopped.

Pathological gambling has been reported before in association with dopaminergic therapy for Parkinson’s disease.1 Almost all of these patients were taking long-term levodopa and some were also taking dopamine receptor agonists such as pergolide and pramipexole. In a number of cases, the appearance of pathological gambling occurred after an increase in dosage of levodopa and/or a dopamine receptor agonist.

It has been proposed that an increase in stimulation of dopaminergic rewards systems is important in the development of pathological gambling and other addictive and compulsive behaviours.

This is probably a very rare adverse effect but prescribers should be alert for its occurrence in patients who are taking combinations of levodopa and dopamine receptor agonists.

Reference
4. Reporting problems with products other than medicines

ADRAC receives reports of suspected adverse reactions in association with medicines, vaccines and complementary medicines. There are also Australian reporting schemes for other products.

*Medical devices:* The Incident Report Investigation Scheme (IRIS) is responsible for the handling and investigation of all reports submitted to TGA on adverse events or problems associated with the use of medical devices. TGA has Incident Reporting forms that are available on request or on the Internet (http://www.tga.gov.au/docs/html/forms/iris_udir.htm). The use of the form is not compulsory. Reports can be made by telephone (1800 809 361), email (iris@health.gov.au), facsimile (02 6232 8555), or post (IRIS, Reply Paid 32, PO Box 100, Woden ACT 2606).

*Agricultural chemicals and veterinary medicines:* The Australian Pesticides & Veterinary Medicines Authority (APVMA) administers a scheme through which adverse effects (in animals, humans or on the environment) in association with agricultural chemicals or veterinary medicines can be reported. Information on the scheme can be found at http://www.apvma.gov.au by selecting “report adverse experiences”.

**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 front of the “Schedule of Pharmaceutical Benefits” and the “Australian Medicines Handbook”, from the Adverse Drug Reactions Unit ☏ 02-6232-8386, or from the website: http://www.tga.gov.au/adr/bluecard.pdf

Reports can also be submitted electronically, by going to the TGA web site (http://www.tga.gov.au) and clicking on “report problems” on the left.

**For further information** from the ADRAC Secretariat:

☎ 1800 044 114  Fax: 02-6232-8392  Email: adrac@health.gov.au

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The Bulletin is also available on the Internet at: http://www.tga.gov.au/adr/aadrb.htm (with complete references)

All correspondence to be addressed to: The Secretary, ADRAC, PO Box 100, Woden, ACT, 2606