

Selective serotonin re-uptake inhibitors in child and adolescent depression

Summary

- The Therapeutic Goods Administration has issued warnings about risks of using selective serotonin re-uptake inhibitor (SSRI) antidepressants in children and adolescents with depression. Antidepressant product information outlines new precautions for this age group. No antidepressant is licensed in Australia for use in children or adolescents with depression.
- There is new evidence of increased risk of suicidality (suicidal ideation, behaviour, and attempts) in children and adolescents, which increases from 2% with placebo treatment to 4% with an SSRI. There were no deaths in the clinical trials reviewed.
- Without convincing evidence of efficacy, the ratio of potential harm to potential benefit is unfavourable for most SSRIs and venlafaxine in child and adolescent depression.
- Psychological therapy (such as cognitive behaviour therapy and interpersonal therapy) is recommended first-line for child and adolescent depression of mild to moderate severity.
- If drug therapy is considered appropriate in severe depression, use with psychological therapy. Monitor response to antidepressant treatment closely with regular review. Discuss the potential for harmful adverse effects with both patients and parents/carers, and explain the need for home and clinic monitoring.
- Fluoxetine has some evidence of efficacy and hence a slightly better benefit:harm ratio than other SSRIs. However, this evidence is not overwhelming; about two-thirds the number who respond to fluoxetine respond to placebo. Fluoxetine is also associated with a risk of increased suicidal ideation and behaviour.
- Heightened suicide risk early in antidepressant treatment is a recognised clinical phenomenon. Trials showing increased suicidality in children and adolescents have mostly been of 8 weeks' duration. Risks of longer-term treatment are unknown.
- Adverse effects such as hyperkinesia, agitation, mania and hostility can occur with the SSRIs, including fluoxetine.
- Tricyclic antidepressants have previously been shown to be no more effective than placebo for children and of limited benefit for adolescents. As regulators could not rule out risks with non-SSRI antidepressants, the precautions for this age group apply to all antidepressants.

Where does the new evidence come from?

Both published and unpublished data held by pharmaceutical companies were reviewed recently by the US Food and Drug Administration (FDA¹) and the UK's Committee on Safety of Medicines (CSM).² The FDA commissioned a re-analysis of adverse event reports from

clinical trials for evidence of self-harm and suicidality (suicidal ideation, suicidal behaviour and suicide attempts). Most trials had been conducted with the incentive from the FDA of patent extensions for carrying out trials in children, regardless of the results — a factor that may have reduced the quality of the trials conducted.³

The FDA reviewed 24 trials involving over 4400 patients treated with nine drugs for major depressive disorder (MDD), obsessive-compulsive disorder (OCD) and other psychiatric disorders. Eleven MDD trials were used in the meta-analysis (n = 2033).⁴ The drugs included the selective serotonin re-uptake inhibitors (SSRIs) citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, and some non-SSRIs (bupropion*, mirtazapine, nefazodone† and venlafaxine).

Efficacy data for SSRIs in OCD, social anxiety disorder and generalised anxiety disorder are not reviewed here. However, in the FDA review the evidence of increased suicidality came from antidepressant use in all indications.

* not licensed for use in depression in Australia.
 † not available in Australia.

What is the advice of regulatory authorities?

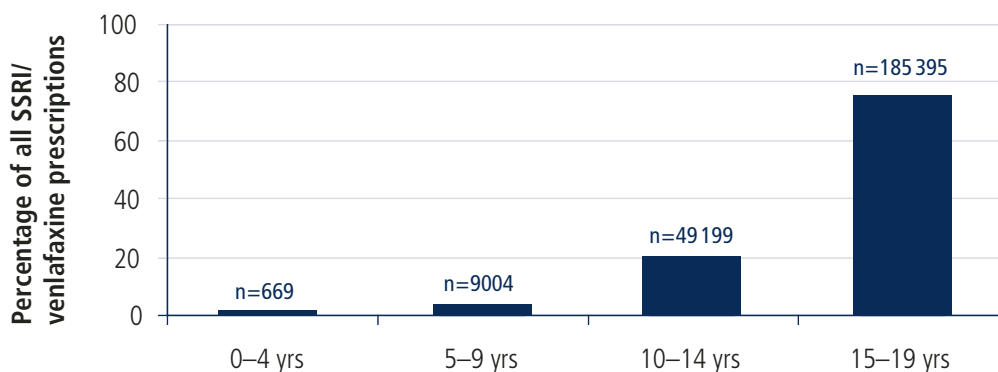
Australia's Adverse Drug Reactions Advisory Committee (ADRAC) warns of the **increased risk of suicidal ideation, suicidal behaviour and self-harm with each of the SSRIs**. The association is apparently strongest with paroxetine and the serotonin–noradrenaline re-uptake inhibitor, venlafaxine.⁵ Drug regulators in the UK, the USA and Europe have issued similar statements.^{2,6,7}

ADRAC recommends that:

- any use of SSRIs in children and young people should take place in the context of a comprehensive management plan and should include careful monitoring for emergence of suicidal ideation, particularly early in therapy or if therapy is interrupted or irregular. Cognitive behaviour therapy (CBT) might enhance the outcome in treatment of depression in this age group

Prescribing of SSRIs to 0–19-year-olds in Australia

Figure 1: SSRI and venlafaxine prescriptions by age group* (%)
 Nov 2003 to Oct 2004



Data provided by Health Insurance Commission, February 2005.

* Prescriptions for citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and venlafaxine to each age group as a percentage of all such prescriptions to 0–19-year-olds. Includes prescriptions for all indications, not only depression. An individual may receive more than one prescription in the time period.

Note: Data for citalopram may be incomplete; prescriptions for citalopram 10 mg include only those dispensed for concession cardholders, as this formulation is below the patient co-payment.

The number of prescriptions to children and adolescents in Australia increases with age, with most (76%) SSRI and venlafaxine prescriptions for adolescents aged 15–19 years. Fewer than 4% of all prescriptions were for children aged less than 10.

- prescribers should be aware of the precautions and warnings made by manufacturers in their product information
- in children and adolescents already being treated with an SSRI, medication should not be withdrawn abruptly.

They also note that:

- the trials reviewed by the FDA were not designed to monitor suicidal events in a systematic way and excluded the most severely depressed patients
- although similar data are not available for other antidepressants, some (such as the tricyclic antidepressants) might also be ineffective, increase suicidality and be more toxic in overdose.

None of the SSRIs or other antidepressants is approved for use in children with major depression, therefore all use is off label.*

The full ADRAC advice is available at http://www.tga.gov.au/adr/adrac_ssri.htm.

Changes to antidepressant product information

The TGA has asked drug sponsors to update their product and consumer medicine information to include the following:

- There are no satisfactory safety or efficacy data for use in children and adolescents
- Regardless of treatment there is a risk of suicidal thinking and suicide attempts for all depressed patients, including adults
- Close monitoring for clinical worsening and suicidality is needed when an antidepressant is first started and when the dose is changed
- Prescribers should review treatment and consider withdrawing the antidepressant if depression is persistently worse, or emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms (see *Information for patients*).

* Off-label use is relatively common for paediatric indications, as clinical trials are seldom available. In this instance, because trial data are available the TGA encourages prescribers to be aware of the findings. In Australia, sertraline (Xydep, Zoloft) and fluvoxamine (Faverin, Luvox, Movox) have approval for use in child and adolescent OCD.

Evidence for antidepressant efficacy is poor — psychological therapy remains necessary

Although small, the increase in risk with the SSRIs occurs in a context of uncertain benefit in paediatric trials. Given the lack of strong evidence of drug efficacy for either SSRIs, mirtazapine, venlafaxine or tricyclic antidepressants, initial treatment of depressed children and adolescents should include addressing environmental factors (e.g. abuse, family conflict), regular monitoring and support, and psychological therapy such as CBT.⁸

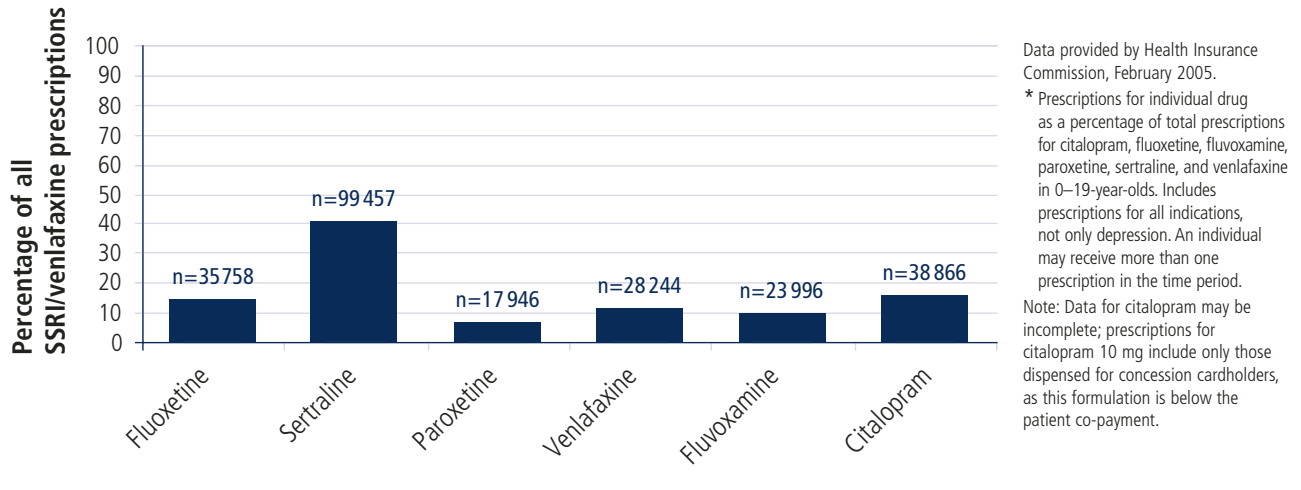
There is a valid concern that the risk of not treating depression also carries potential for harm⁹⁻¹¹, particularly as specialised child and adolescent mental health services are often difficult to access. Although placebo effects in depression trials are substantial, it is worth noting that placebo treatment is not the same as doing nothing. At the very least, patients on placebo treatments in trials receive regular monitoring, support, encouragement to continue treatment and reinforcement. Other non-drug interventions might include encouraging the use of a confidante or journal; prescribing sleep hygiene, exercise and other activities; and psychoeducation.

The NHMRC guidelines for managing depression in young people contain useful information on non-pharmacological measures (although out of date with respect to prescribing information).¹²

When non-drug treatment is ineffective, use of fluoxetine might be considered with informed parental support, home monitoring and regular clinician contact. Ideally, SSRIs should be prescribed in consultation with a child and adolescent psychiatrist, but this may not always be possible.

Practical advice for GPs is available from beyondblue (<http://www.beyondblue.org>).

**Figure 2: SSRI and venlafaxine prescriptions to 0–19-year-olds in Australia by drug*
Nov 2003 to Oct 2004**



SSRIs have uncertain benefits in child and adolescent depression

Although its recent review focussed on suicidality and self-harm, the FDA noted concern about the lack of efficacy data in trials of SSRI therapy in child and adolescent depression. Of studies submitted to the FDA under its paediatric trials incentive, only 20% had positive results, with only fluoxetine gaining a US licence for use in children.³

A review of published and unpublished data for all SSRIs in this age group found that the balance of benefit and harm was favourable only for fluoxetine (see below).^{2,13} The fact that unfavourable or negative data tend not to be published has been highlighted in discussions about these drugs.^{2,13,14}

There is minimal evidence of efficacy for most SSRIs in children and adolescents. Effect sizes tend to be small to moderate¹³; when statistically significant differences have been shown, they are mostly of uncertain clinical significance.

Sertraline is the SSRI most frequently prescribed for children and adolescents in Australia, accounting for 41% of SSRI/venlafaxine prescriptions in this age group (figure 2). In data aggregated from two trials, response* was achieved in 69% of sertraline-treated patients vs 59% of placebo-treated patients.¹⁵ Differences in

depression symptom improvement were of unlikely clinical value, despite statistical significance (mean changes in scores on the Children’s Depression Rating Scale — Revised [CDRS-R]: sertraline 22.8 vs placebo 20.2, $p = 0.007$).

A citalopram trial found differences of about 6 points ($p < 0.05$) between drug and placebo on mean CDRS changes, again of relatively small clinical importance, and no difference in Clinical Global Impression (CGI) improvement ratings (47% for citalopram vs 45% with placebo).¹⁶

Venlafaxine and paroxetine appear to have the least favourable benefit:harm ratios.^{2,5,13} Pooling published and unpublished data for paroxetine showed little evidence of efficacy, but did reveal an increase in serious adverse events (12% paroxetine vs 4.4% placebo) and suicidal ideation or attempts (3.7% paroxetine vs 2.5% placebo).¹³ Similarly venlafaxine showed little effect on depression but an increased risk of adverse events and suicide-related events (7.7% venlafaxine vs 0.6% placebo).¹³ Together these two drugs make up about 20% of all SSRI and venlafaxine prescribing in 0–19-year-olds in Australia (figure 2).

Tricyclic antidepressants have previously been shown to have no benefit over placebo for children and limited benefit for adolescents.¹⁷ They are also more toxic in overdose.

Is fluoxetine any different?

Drug evaluators suggest that fluoxetine may have a better benefit:harm ratio than other SSRIs^{2,5}, based on slightly better evidence of efficacy in three randomised, placebo-controlled trials (n = 754).¹⁸⁻²⁰

Overall, the results for fluoxetine suggest that it can improve major depression in children and adolescents. However, it may not work in all patients and, in a small number, might induce or intensify suicidal ideation or behaviour.

Across the three trials, the criteria for response were met in 52–56% of fluoxetine-treated patients compared with 33–37% on placebo.[†] As with other SSRIs, the single-item clinician rating of improvement used to measure response* was more favourable than for depression symptoms[‡] — these improved with both fluoxetine and placebo, with small differences in the average amount of improvement. Further, the response to placebo in these trials was roughly two-thirds of the rate for active treatment.¹⁸⁻²⁰

In the first trial to directly compare combined treatment with drug or behavioural therapy in adolescents, the Treatment for Adolescents with Depression (TADS) trial compared fluoxetine with placebo, CBT alone, or fluoxetine plus CBT.¹⁸ About one-third of subjects had a clinically significant degree of suicidal ideation at baseline, but high-risk patients were excluded.

In the TADS trial, fluoxetine + CBT resulted in a statistically higher response rate* (71%) than either CBT (43%) or placebo alone (35%) but not fluoxetine alone (61%). Combined therapy was more effective in reducing symptoms, and self-reported suicidal ideation[§] improved more than with placebo or fluoxetine alone. The authors suggest a protective effect for CBT against suicidal ideation.²⁰

However, a weakness of the TADS trial design was a lack of blinding in the drug + CBT group (these patients knew they were receiving fluoxetine) and in the CBT-only group (these patients knew they would not receive medicine). As placebo effects tend to be strong in antidepressant trials, this may explain why there was no difference between CBT-only and placebo for most outcomes.

For fluoxetine treatment alone, results were equivocal. Clinician-rated response was better than for CBT-only or placebo. However, the degree of improvement in symptoms from baseline to study-end differed little between fluoxetine and placebo despite statistical significance (mean change on the CDRS-R of 19 points for placebo, 22 points for fluoxetine alone, 27 points for fluoxetine + CBT; the maximum possible change was 96 points).

Any fluoxetine treatment increased the risk of harm-related adverse effects, including self-harm and suicidal ideation (odds ratio: 2.19 [95% confidence interval (CI) 1.03 to 4.6]) and of other psychiatric adverse events, including mania, agitation, fatigue and insomnia.

* The criterion for 'response' was a rating by the assessing clinician of 'much improved' or 'very much improved' on the Clinical Global Impression (CGI) improvement scale.

† Unlike the sertraline and citalopram trials, the fluoxetine trials included children with attention-deficit hyperactivity disorder (ADHD) and 'conduct disorder'.

‡ Measured with the Children's Depression Rating Scale-revised (CDRS-R).

§ Measured by the Suicidal Ideation Questionnaire — Junior high school version (SIQ-Jr).

What is the evidence of potential harm?

The FDA analysis found an estimated risk increase for suicidality from 2% with placebo to 4% with an SSRI, across trials for all indications.¹ Among individual drugs there is some indication of greater risk of suicidal ideation and behaviour for paroxetine and venlafaxine compared with placebo (relative risks: 2.65 [95% CI 1.00 to 7.02] and 4.97 [95% CI 1.09 to 22.72], respectively), and of increased agitation/hostility with paroxetine, but the precise estimates are not reliable because of small numbers.^{4,21}

These risks were found in trials:

- that were not designed to measure suicidality
- in which reporting of suicidal thoughts or behaviours was incidental rather than systematic
- that excluded those at high suicide risk
- in which the number of events was small.

These factors mean that the accuracy of the risk estimates and any mediating factors are uncertain.

Information for patients

- Provide information about depression, non-drug treatment options and the role of antidepressant drugs in the overall treatment of depression.
- Ensure that patients know how to access help if urgently required (including after hours).
- If an antidepressant is prescribed, advise patients and carers of the potential benefits and harms of drug treatment and of the need for monitoring at home and with their doctor.
- Inform patients and carers not to stop taking these drugs suddenly but to seek advice about tapering the dose to minimise withdrawal effects.
- Clinicians, carers and patients should be alert to the emergence of the following, especially during early antidepressant treatment and when the dose is adjusted:
 - new or more thoughts of suicide, or suicide attempt
 - new or worsening depression
 - new or worse anxiety
 - agitated or restless feelings
 - panic attacks
 - sleeping difficulties
 - new or worse irritability
 - aggressive, angry or violent behaviour
 - acting on dangerous impulses
 - hyperactive action or speech (hypomania or mania)
 - other unusual changes in behaviour.²²

These changes may occur on a day-to-day basis and may be abrupt. Symptoms, particularly those that are 'severe, abrupt in onset, or were not part of the patient's presenting symptoms are cause for concern'.⁶ It is suggested that patients see their doctor weekly for the first four weeks, fortnightly for the next month, and then after 12 weeks of treatment.

The beyondblue website has an area for young people with depression, as well as information for parents (<http://www.beyondblue.org.au>).

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.