



CLINICAL GUIDANCE ON THE USE OF ANTIDEPRESSANT MEDICATIONS IN CHILDREN AND ADOLESCENTS

Purpose

This statement is addressed to prescribers, especially general practitioners, and is intended to provide clinical guidance on the use of Selective Serotonin Reuptake Inhibitors (SSRIs) when treating children and adolescents. While treatment of psychiatric and developmental disorders in children may include multiple modalities of therapy, this statement is focussed on medication.

Background

A recent re-analysis by the FDA of adverse events reported in trials of antidepressants in children and adolescentsⁱ concluded that the risk of treatment-emergent suicidal thinking or behaviour was increased in patients on active drug (up to 4%) compared to those taking placebo (up to 2%). There may be an interactional effect between medication and the underlying condition, since the effect is more marked in depression than in anxiety disordersⁱⁱ. There may also be an age effect, with adolescents more affected than pre-adolescents. However, there are insufficient data to make conclusions on these factors at this point. It is important to note that there have been no completed suicides in any clinical trial subject. Further, there is indirect evidence to suggest that, at a general population level, the use of SSRIs may have been associated with a reduction in overall suicides.ⁱⁱⁱ

We believe it is important that children and adolescents continue to have access to these medications. As with any prescribing decision, the potential risks need to be balanced against the potential benefits, and should take into account evidence from controlled trial data, as well as the particular clinical circumstances of the individual patient.

Major depressive disorder is a serious condition which is both debilitating and potentially lethal in its own right. Psychosocial development may be compromised by untreated depressive illness. Untreated depression is associated with significant rates of suicidal ideation and behaviour, and with completed suicide. Not treating depression is more likely to result in harm than is appropriate use of antidepressants.

We support and endorse the contents of the Australian Adverse Drug Reactions Advisory Committee's revised statement of 15 October 2004 on the use of SSRI antidepressants in children and adolescents^{iv}. In New Zealand, Medsafe have issued a similar statement which is in broad general agreement with the advice from ADRAC. These statements outline rational clinical practice given the current knowledge base, and include:

1. Any SSRI use in adolescents with Major Depressive Disorder (MDD) should be undertaken only within the context of comprehensive management of the patient.

Such management should include careful monitoring for the emergence of suicidal ideation and behaviour.

2. The choice of SSRI for adolescents should be made taking into account the recent evaluations of clinical trial data and product information. Note that the current Australian product information for SSRIs recommends against their use in children and adolescents and that no antidepressant currently has an indication for the treatment of depression in children and adolescents.
3. Adolescents who are currently being treated for MDD with an SSRI should not have their medication ceased abruptly.

General points

- Cases of children and adolescents presenting with emotional-behavioural symptoms are complex and their assessment takes time and expertise. Ideally and wherever possible, children and adolescents with the more severe or complex forms of depression or anxiety disorders should be reviewed by a child and adolescent psychiatrist at some point in their illness. However, it is recognised that access to these services is limited and that in practice it is often the general practitioner or paediatrician who will make decisions regarding pharmacological management.
- While further research is needed, the available evidence suggests that for selected patients antidepressants are a necessary component of the successful treatment of certain depression and anxiety disorders in children and adolescents. The more severely ill patients, those with bipolar disorder, and those who fail to respond to adequate psychological management are more likely to require antidepressant treatment. The current evidence suggests that fluoxetine has the most favourable risk/benefit profile and should be considered as the antidepressant of choice. However, not all patients will tolerate or respond to fluoxetine. In this situation, other SSRIs should be considered, remembering that the evidence for the efficacy of other SSRIs is at this stage not established.
- There are insufficient data to differentiate the risk/benefit profiles of different SSRIs in different conditions. Although clearer distinctions in effects between particular drugs may emerge over time, we believe at present it is best to consider this class of drugs as a group.
- When children and adolescents are commenced on an SSRI, we recommend:
 - Starting with a low dose and building up gradually,
 - Warning parents and patients about potential activation symptoms, including the possible emergence of suicidal thoughts early in treatment,
 - Careful monitoring in the early weeks for the emergence of behavioural activation, with the prescriber being available for contact,
 - Consultation, wherever possible, with a child and adolescent psychiatrist or developmental paediatrician in the case of non-response or significant

deterioration. This may be done by telephone or teleconferencing (where available) if review in person is impractical,

- Following recovery, the antidepressant should be continued for a period of six to twelve months to prevent relapse or recurrence.
- Sudden cessation of SSRIs should be avoided in order to avoid discontinuation syndrome
- Tricyclics and MAOIs have a generally higher risk of adverse effects and much greater toxicity in overdose. Prescribing of these antidepressants for MDD to children and adolescents should not be initiated by general practitioners.
- It is important that adverse events from the use of antidepressant medications in children and adolescents are reported to ADRAC in Australia or CARM in New Zealand.
- More research is needed into the use of psychotropic medications in children and adolescents with a range of conditions. Trials should be of sufficient duration to detect both benefits and risks into the medium term. More research is also required regarding the efficacy of psychological-based therapies.
- Particular caution is needed in the case of very young children (under five). These children should not be prescribed psychotropic medication unless they are reviewed, and continue to be monitored, by a child psychiatrist or paediatrician.

Use of antidepressants in children and adolescents

A. ANXIETY DISORDERS

The main indication for the so-called antidepressant class of medications in children and adolescents is anxiety disorders, including obsessive compulsive disorder, generalised anxiety disorder and social phobia.^{v, vi} Cognitive behaviour therapy (CBT) is often effective in these conditions; however, when patients have severe functional impairment (social, academic), SSRI medication should be considered.

B. MAJOR DEPRESSION

The evidence for the effectiveness of antidepressant medication in children and adolescents with major depression is less strong, with generally modest effect sizes. However, it must be remembered that the most severe patients are usually excluded from clinical trials. This and other methodological issues may limit the extent to which currently available clinical trial data can be applied to the clinical population.

Medication is generally not recommended as first line treatment for children and adolescents with mild to moderate depression. In this less severely ill population, CBT or other appropriate psychological management is the treatment of choice. The combination of SSRI medication and CBT is the most effective treatment for moderate to severe major depression in adolescents.^{vii}

C. DEVELOPMENTAL DISABILITIES

Anecdotal clinical practice and open label trials suggest that antidepressant medication can be very effective in reducing emotional lability and obsessionality in children and adolescents with severe developmental disabilities, including autistic spectrum disorders.^{viii} SSRIs appear to enable more adaptive social functioning in many of these patients.

ⁱ Mosholder AD. Suicidality in pediatric clinical trials of antidepressant drugs: comparison between previous analyses and Columbia University classification. Centre for Drug Evaluation and Research, Food and Drug Administration, 16 August 2004.

<http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-11-TAB09a-Mosholder-review.pdf>

ⁱⁱ Medicine & Healthcare Products Regulatory Agency, Committee on Safety of Medicines. Selective Serotonin Reuptake Inhibitors (SSRIs): Overview of regulatory status and CSM advice relating to major depressive disorder (MDD) in children and adolescents including a summary of available safety and efficacy data. December 2003

ⁱⁱⁱ Gunnell D. Ashby D. Antidepressants and suicide: what is the balance of benefit and harm BMJ 2004. 329(7456):34-8.

^{iv} Adverse Drug Reactions Advisory Committee Use of SSRI antidepressants in children and adolescents. Updated 15 October 2004 http://www.tga.gov.au/adr/adrac_ssri.htm

^v The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. New England Journal of Medicine. 2001;344(17):1279-85.

^{vi} Geller DA, Biederman J, Stewart SE, Mullin B, Martin A, Spencer T, Faraone SV Which SSRI? A Meta-Analysis of Pharmacotherapy Trials in Pediatric Obsessive-Compulsive Disorder. Am J Psychiatry 2003;160:1919-1928.

^{vii} March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J. 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. JAMA 2004. 292(7):807-20

^{viii} Namerow LB, Thomas P, Bostic JQ, Prince J, Monuteaux MC. Use of citalopram in pervasive developmental disorders. Journal of Developmental & Behavioral Pediatrics. 2003;24(2):104-8.

National Institute of Clinical Excellence. Depression in children: identification and management of depression in children and young people in primary care and specialist services.

<http://www.nice.org.uk/page.aspx?o=33920>