

Evidence Summary: Using SSRI Antidepressants and Other Newer Antidepressants to Treat Depression in Young People: What are the issues and what is the evidence?



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Why is there so much debate on this issue?

Concerns about using Selective Serotonin Reuptake Inhibitors (SSRIs) in young people centre on two issues. First, SSRIs might be less effective than first thought for treating adolescent depression. Second, SSRIs might be associated with worrying side-effects. The latter concern first emerged in light of evidence indicating an increase in suicidal ideas and behaviours among people aged 12-18 years who were prescribed SSRIs for the treatment of depressive illnesses (1-4). This led to a 'black box warning' in the United States cautioning clinicians about using this class of medication for young people aged up to 24 years. In Australia, no antidepressant (including any SSRIs) is currently approved by the Therapeutic Goods Administration (TGA) for the treatment of major depression in people aged less than 18 years (5). As a result of the warnings and associated publicity, SSRI prescription rates were observed to decline among young people in many countries (6). However, an association has recently been drawn between these declining rates of prescriptions and an increased suicide rate over the same period of time (6). One study has shown that there has been no increase in psychotherapy referrals to compensate for the decreasing prescription rates (7), suggesting that there has been a reduction in interventions generally for young people with depression, rather than SSRI prescriptions specifically.

There continues to be strong debate on this topic, with many clinical researchers arguing that SSRIs are essential for treating depression in this age group, (8-12) while others claim the contrary (13-14). What further complicates this issue is the potential for bias to be introduced into this debate if only positive findings from SSRI drug trials are published in peer-reviewed journals, which was certainly the case in the past (15).

What are evidence based guideline recommendations for the use of medication?

Current international clinical practice guidelines highlight fluoxetine as the only SSRI with approval from the USA Food and Drug Administration (FDA) (17,18). The FDA has also recently approved escitalopram. In Australia, guidelines published in 2011 by beyondblue and the National Health and Medical Research Council indicate that fluoxetine should only be considered for young people with moderate to

severe depression (not mild depression) when psychological therapy has not been effective, is not available or is refused or if symptoms are severe (16). The guidelines state that prescription must occur in the context of an ongoing therapeutic relationship and management plan. Guidelines also recommend close monitoring of symptom severity and adverse effects, including the onset or increase in suicidal thinking especially in the first 4 weeks of commencing medication, and that there be a protocol in place for managing suicidal thinking.

Are SSRIs and Newer Antidepressants effective for young people? What is the evidence?

Additional evidence is available since the publication of the Australian guidelines in 2011. The results of a recently published Cochrane systematic review (15) show modest effects of antidepressants compared with placebo in improving depression. The rates of remission while on an antidepressant were 448 per 1000 compared to 380 per 1000 in the placebo group¹.

Despite the evidence supporting fluoxetine (and more recently escitalopram has received FDA approval), the Cochrane review showed the effects for these medications were similar to others included in the review². The overall reduction in depression severity scores on the Children's Depression Rating Scale-Revised (CDRS-R) was 5.63 lower for fluoxetine and 2.67 for escitalopram compared with those on placebo (from a possible range of 17-113) and unlikely to indicate significant clinical change for the majority of young people. For fluoxetine, the number needed to treat for an additional beneficial outcome (NNTB)³ of remission is 6. Rates of remission were not significantly improved on escitalopram compared with placebo. Across all SSRIs, the NNTB⁴ is 15.

What kinds of patients were included in the trials that were included in the review?

It is important to note that the majority of clinical trials have excluded young people with more severe forms of depression, including those with comorbid mental health disorders (including substance use disorders) and those with suicidal ideation or deliberate self-harm. The extent to which SSRIs

1. Rates of remission are based on the median remission rate in the placebo groups post intervention.

2. Newly available data for duloxetine on the www.clinicaltrials.gov website were not available at the time of the Cochrane update.

3. NNTB is based on an assumed control risk for a group of moderately depressed young people (based on the median remission rate in the placebo group).

4. Overall NNTB calculated in the same manner as point 3 above.

are effective for treating depression in these patients, who commonly present in specialist clinical settings, is unknown. There is very little research evidence to guide practice for this group of young people.

What is the evidence regarding the risks of using SSRIs?

The results of several systematic reviews (4,10,15) demonstrate that there is an increased risk of both suicidal ideation and suicidal behaviour for young people treated with an SSRI compared with those receiving placebo. Across all SSRIs, the risk of a suicide related outcome for those taking antidepressants was 58% higher (risk ratio 1.58, 95% CI 1.02 to 2.45), compared with those taking placebo. This equates to an increased risk in a group with a median baseline risk from 25 in 1000 to 40 in 1000 (15). For fluoxetine, the number needed to treat for an additional harmful outcome (NNTH)⁵ of suicidal ideation/behaviour is 32. Across all SSRIs, the NNTH⁶ is 66. No deaths have been reported that are attributable to SSRI prescription.

What does all this mean about treating a young person with depression?

There is evidence that fluoxetine is modestly effective for reducing symptoms of depression in young people. Balanced against these findings are the even greater risks of not treating depression, be it pharmacological or psychological.

There is a clear imperative to engage young people who are experiencing a depressive disorder in good clinical care. Clinicians can consider a range of evidence-based interventions, including those that are relatively simple. For example in the recent ADAPT trial, which compared fluoxetine with fluoxetine plus cognitive behaviour therapy (CBT), 21% of young people accepted into the trial responded to a brief psychosocial intervention and subsequently had to be excluded from the study before randomisation (19). Trials such as ADAPT demonstrate that a high level of 'standard care', which might or might not include medication, is sufficient for many young people, including those experiencing moderate to severe depression (19-21). There is also evidence that psychological therapies, such as CBT and interpersonal therapy (IPT) can be effective for some young people, at least in the short term (22).

Overall, a stepped model approach is recommended for the treatment of depression in young people (17,18), whereby clinicians consider commencing treatment with a psychological therapy, such as CBT or IPT. This is especially the case for young people with mild depression. In cases of moderate to severe depression, SSRI medication might be considered within the context of comprehensive management of the patient, which includes regular careful monitoring for the emergence of suicidal ideation or behaviour (17).

Irrespective of the treatment chosen, it is essential that there is close monitoring of the young person's symptoms, and any side effects if medication is prescribed. This also helps to form the basis of ongoing collaborative discussions with the young person and their families and supporters where appropriate, about further treatment options for those who do not respond to initial treatment (including the use of increasingly complex interventions or medication).

Keeping up with new findings?

There are a number of sources of up-to-date information about the effectiveness of interventions for treating depression. The Centre of Excellence in Youth Mental Health will continue to update information about effective interventions for youth mental health disorders www.headspace.org.au/what-works

For more information, the beyondblue Clinical Practice Guidelines: Depression in Adolescents and Young Adults can be downloaded at: www.beyondblue.org.au/index.aspx?link_id=6.1247

Other useful sites include:

The Cochrane Library - Australian Access www.cochrane.org.au

The Centre for Evidence Based Mental Health cebmh.warne.ox.ac.uk/cebmh/cebmh.htm

The York Centre for Review and Dissemination www.york.ac.uk/inst/crd

For more general information about principles and practice of evidence based medicine go to: The Centre for Evidence Based Medicine in Oxford www.cebm.net.

5. NNTH is based on an assumed control risk for a group of young people with moderate severity of suicidal ideation/behavior (based on the median rate in the placebo group)

6. Overall NNTH calculated in the same manner as point 5 above.

* This evidence summary replaces the previous "Evidence Summary: Using SSRI Antidepressants to Treat Depression in Young People: What are the Issues and What is the Evidence?". It contains updated content and trial data, and is current as of December 2012.

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