Should young people be given antidepressants?

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YES Depression and obsessive-compulsive disorder cause considerable distress in young people. These disorders affect emotional, educational, and social development. To deny these vulnerable groups the possibility of receiving antidepressants would be to withhold one of the few evidence based treatments available to them.

There are genuine reasons to question their use. Nevertheless, the evidence indicates that the benefits of these drugs outweigh the risks when used in the appropriate clinical context. I shall focus on the use of selective serotonin reuptake inhibitors (SSRIs) because this is the group of antidepressants for which the evidence in young people is strongest¹ and it is the use of these drugs in depression that has been most controversial.

Quality of evidence

The criticisms of research into SSRIs include an exaggerated description of efficacy, selective reporting of measures, short follow-up periods, poor reporting of adverse effects, and underplaying the large placebo effects.² Participants were mostly recruited by advertising and self referral³ and common comorbidities, including suicidality, were excluded.⁴ In the first half of the decade there was also selective publication of studies with more positive results.⁵

However, objective meta-analysis of the studies shows a significant benefit over placebo for some SSRIs.^{1 5} It is not surprising then that the Medicines and Healthcare Regulatory Authority⁶ and the National Institute for Health and Clinical Excellence (NICE)¹ both concluded that SSRIs can be used for the treatment of depression in young people. Recent studies without many of the earlier methodological flaws—for example, the adolescent depression antidepressant and psychotherapy trial (ADAPT)⁷—have added further evidence to support the use of SSRIs in treating depression.

Risks and benefits

So, if the drugs work, what about the risks? Earlier publications tended to play down the

risks, particularly that of increased suicidality. When this came to light there was an understandable flurry of adverse publicity. However, a meta-analysis that included previously unpublished studies showed the benefits outweighed the risks, at least for fluoxetine.⁵ A more recent meta-analysis confirms an increase in suicide related events in young people with depression taking SSRIs compared with placebo, but the difference is small (4.8% v 3%) and there have been no suicides in any of the studies to date.⁴ Two studies found a decrease in suicidality with fluoxetine during treatment.⁷ Overall, although there is an increase in suicidality, the risk is small and can be reduced further by careful monitoring.

Evidence for other treatments

Are there other treatments for depression in young people that make the use of antidepressants unnecessary? There is some evidence for the efficacy of psychological treatments such as cognitive behaviour therapy, interpersonal therapy, and family therapy, but the effects

are small. The treatment for adolescents with depression study (TADS) suggested that cognitive behaviour therapy alone was no different from placebo and was a significantly poorer treatment than SSRIs alone.⁸ NICE, partly in consideration of evidence from TADS that suggested cognitive behaviour therapy combined with SSRI reduced suicidal behaviour, supported the use of psychological therapy as first treatment of moderate or severe depression but was clear that fluoxetine should be offered if the young person does not respond.¹

Two studies reported since the publication of the NICE guideline have shown no benefit for combined treatment over SSRIs alone.^{9 10} In patients with moderate to severe depression ADAPT found no added value in combining cognitive behaviour therapy with fluoxetine.⁷ These studies support the case for fluoxetine alone being the treatment of choice for more severe depression.

Obsessive-compulsive disorder

Antidepressants are also used to treat obsessive-compulsive disorder. NICE included 14 randomised controlled trials in its analysis of the efficacy of SSRIs for obsessive-compulsive

disorder in young people.¹¹ It concluded that the evidence supported the use of SSRIs and recommended fluvoxamine or sertraline, which have been licensed for this disorder. It found no significant increase in suicidal behaviour but, because of remaining uncertainty about risk, recommended cognitive behaviour therapy as the first line treatment. NICE also recommended the use of the tricyclic antidepressant clomipramine if SSRIs are ineffective.

Informed choice

Worrying methodological errors, publication bias, and omissions of evidence in the conduct and reporting of some SSRI trials have rightly alarmed the medical profession and the public. However, careful and objective review of the evidence shows that antidepressants have a place in treating young people with depression or obsessive-compulsive disorder. Parents and young people need to be told the risks and benefits, given advice, and be supported in choosing an evidence based treatment. Removing antidepressants from this choice would take away one of the few potentially effective interventions for these disabling conditions.

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Depression is disabling a growing proportion of children, but evidence on treatment is disputed. **Andrew Cotgrove** believes drugs are a vital part of the armoury but **Sami Timimi** is unconvinced that they are helpful or safe

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NO The medical profession had endorsed the use of selective serotonin reuptake inhibitors (SSRIs) well before any of the big studies in children were published.¹ Now that studies have been done, the evidence is clear: the drugs are not effective in young people and can increase suicidal behaviour. Continuing to use SSRIs in young people is not good value for money, dangerous, and ethically unsound.

It is well established that tricyclic antidepressants are not effective for childhood depression.² The evidence suggests SSRIs are no better. None of the studies on SSRIs for childhood depression have, on outcome measures reported by patients or parents, showed significant advantage over placebo.³ No data regarding rates of self harm, presentations to emergency or mental health services, or school attendance were presented in any of the studies, leading the reviewers to conclude that investigators exaggerated the benefits and downplayed the dangers of SSRIs for children. A subsequent systematic review found that unpublished trials showed

that newer antidepressants were even less effective and more harmful for children than suggested by the published trials.⁴

Despite this, one antidepressant, fluoxetine, was spared. National guidelines concluded that it was the only antidepressant with a favourable balance of benefit over risk.⁵ Given its similar pharmacological properties, there is no theoretical reason why fluoxetine should have a significantly different profile from other SSRIs; and indeed it doesn't. The treatment of adolescent depression study (TADS)⁶ is the most influential study backing fluoxetine and provides a good example of how the publicity does not match the published findings.

Misrepresentation

The investigators claimed to show an advantage for fluoxetine, especially when combined with cognitive behaviour therapy. However, the way they reported their data was flawed.⁷ The study included a double blind comparison of fluoxetine against placebo and an unblinded comparison between cognitive behaviour therapy alone and fluoxetine with cognitive behaviour therapy. The lack of patient blinding and placebo control in the last two groups is likely to exaggerate the benefit seen in participants receiving fluoxetine with cognitive behaviour therapy because they had more face to face contact and knew (as did their doctors) that they were not receiving placebo. Furthermore, the poor response in the group receiving only cognitive behaviour therapy is inconsistent with other published studies, raising questions about the quality of the psychotherapeutic intervention in this study.

Comparing results across all four groups is therefore misleading. The valid finding from the study is the lack of a statistical advantage for fluoxetine over placebo on the primary end point, the children's depression rating scale. Despite the exclusion of known suicidal behaviour, the study found a trend to more suicidal behaviour (six attempts in the fluoxetine groups versus one in the no fluoxetine groups). This result is consistent with that of other trials of SSRIs. Putting together that result with the lack of clinically important advantage over placebo on most measures and similar findings in the previous studies comparing fluoxetine and

placebo,⁸ the profile for fluoxetine is similar to that of all other SSRIs—it has little efficacy and is potentially dangerous.

However, we should spare a thought for the beleaguered doctor. Given the high placebo response, many doctors will see improvements after prescribing an antidepressant for a young person in distress and subsequently attribute improvements to the drug. This high placebo response may thus reinforce prescribing, and it has been difficult for many doctors faced with a distressed young person to accept that SSRIs may be ineffective.

Role of journals

Distorted reporting hasn't helped this situation. Major medical journals have published papers on antidepressants for children in which the message (affirmations of efficacy and safety) is at odds with the reported outcomes (of no statistical significance, dubious clinical importance, and increased rates of suicidal behaviour). Thus many of the abstracts do not mention lack of significance on the primary measures. Others such as the recent adolescent depression antidepressant and psychotherapy trial (ADAPT)⁹ didn't even include a placebo arm, giving the (false) impression that SSRIs have already been shown to be more effective than placebo.

Thus marketing spin has taken precedence over scientific accuracy. One reason for doing the studies in the first place was to justify well established prescribing patterns.

It created a trend which has become difficult to reverse despite the evidence. But reverse it we must, as it is neither value for money nor clinically useful, may have resulted in a small but tragic number of avoidable suicides, and contributed to a trend of inappropriately medicalising common emotional states and experiences.¹⁰ Most states of childhood distress are self limiting and do not require extensive intervention, but when intervention is necessary psychotherapy has a well established record of effectiveness.¹¹

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References are on bmj.com

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