

Suicide and antidepressants in children

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(See 'Children, serotonin and suicide')

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- Antidepressants are not first-line treatment for children and adolescents.
- They cause a small but significant increase in suicidal thinking and self-harm behaviour.
- Unless there is acute risk, consider education and 'watchful waiting'.
- Report all possible adverse events to the Australian Adverse Drug Reactions Advisory Committee.

Although selective serotonin reuptake inhibitors (SSRIs) have not been approved for use in children under 18 years old, they are widely used in general practice. Until 2003, most authorities argued that these drugs, which are relatively non-toxic in overdose, were without significant undesirable adverse effects, and therefore safe for childhood depression. It is now apparent that the data were biased, giving an overly positive view of efficacy and underplaying adverse effects including increased suicidal risk.¹ Having re-examined the data, UK regulators have contraindicated all antidepressants other than fluoxetine for children. In the USA, the Food and Drug Administration (FDA) applied a 'black box warning' to the product information of

all antidepressants to warn prescribers and consumers of the increased suicide risk in children.

There have been eight published and 16 unpublished randomised controlled trials of newer antidepressants in children.² None of the unpublished and only half of the published studies have shown any advantage over placebo on the pre-specified primary outcomes. Only one-third of all published measures (all of these physician-rated rather than self- or parent-rated) favour drug over placebo. In most of these cases placebo accounted for about 85% of the overall response, suggesting that the benefit of the antidepressant drugs was of dubious clinical significance. Although trials such as the Treatment of Adolescents with Depression Study³ have supported claims that antidepressants are beneficial, these claims are often based on flawed interpretations of data.⁴

If evidence for effectiveness is weak, what of harm? FDA analysis (and re-analysis by Columbia University) showed that during the 6–12 weeks of the randomised controlled trials, the risk of suicidal activity/thinking was 4% for those on medication and 2% for those on placebo. This is a statistically significant difference.⁵ Two studies^{2,6} exempted fluoxetine from conclusions that the harm:benefit ratio was unfavourable; our analysis did not.¹ Subsequently, the FDA deemed that no individual antidepressant is exempt from concerns about suicide.⁷ There is no evidence that older adolescents are less at risk than younger. Studies showing no overall increase in suicide in response to these drugs in adults cannot reassure us that the risks for adolescents decrease as they approach 18 years of age. If young adults on antidepressants had a higher risk of suicide than older people, this might not be detected as a change in the suicide risk in the adult population as a whole. The UK product information warns that paroxetine carries 'a possibility of an increased risk of suicide related behaviour in young adults ages 18–29'.

There is a plausible argument that any increased risk in the short time frame covered by randomised controlled trials is outweighed by subsequent reduction in suicide due to effective treatment of depression. Some have attributed reductions in suicide rates over the last decade to the increased availability of SSRIs, but there are reasons to doubt this association.⁸

Many adverse effects of new drugs (especially those not

In this issue...

Australian Prescriber was first published 30 years ago. Although the journal had a turbulent development, it survived to become an important part of Australian practice.

Unfortunately, some Australian children do not survive their adolescence because of depression. Awareness of childhood depression is increasing, but its management is controversial. Joseph Rey, Jon Jureidini and Anne Tonkin take two views of the evidence concerning antidepressants, while Philip Hazell gives an overview of the role of psychotropic drugs in children.

Despite improvements in the last 30 years, the health of Indigenous Australians remains a problem. Although medicines are only part of the solution, it is important to use them appropriately. Cathy Larkin and Richard Murray provide advice on how to achieve this.

predictable from the mechanism of action of the drug) do not emerge until well after marketing approval. As the number of people involved in randomised controlled trials (in this case, just over 4000) is so much smaller than the number of patients who ultimately take the drug, infrequent adverse events often only emerge after years of widespread use. Unfortunately, postmarketing surveillance is poorly implemented internationally. It is the weakest function of the FDA (as shown by the withdrawal of rofecoxib). In Australia reporting of adverse events to the Adverse Drug Reactions Advisory Committee (ADRAC) is voluntary, yet SSRI rate among the highest for adverse events notified (5% of the total number of notifications since 1972).

So we have poor evidence of efficacy, small but significant increases in suicide risk, and significant, probably underestimated, adverse events. The evidence therefore shows us that antidepressants are not demonstrably 'better than nothing' and may be worse. This conclusion will be at odds with many general practitioners' clinical experience in using these drugs. The discrepancy arises because prescribers who have seen apparently positive responses to antidepressants have not realised that much of the observed benefit would have occurred in response to a placebo.

So what should general practitioners do when faced by an apparently depressed adolescent? Recent recommendations from the UK National Institute for Clinical Excellence confirm that antidepressants are not appropriate for the treatment of mild depression in any age group.⁹ Their proposed strategy of 'watchful waiting' is appropriate for children with mild-moderate depression. Where acute risk is low, a general practitioner might offer a brief explanation about depression, sleep hygiene, the usefulness of finding a confidante, the benefits of exercise and of gradually resuming any activities set aside because the individual is 'too depressed'. The general practitioner should then arrange to see the patient again in about two weeks but offer to talk to them earlier if they are worried.

In more severe cases, referral to or consultation with a child and adolescent mental health service or a child psychiatrist is recommended. The limited availability of such services is an indication for advocacy; it does not mandate prescribing against available evidence. Such prescribing, based on faith or hope that antidepressants may actually be better than the evidence indicates, risks contravening the injunction to 'first do no harm'.

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Children, serotonin and suicide

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Controlled trials show that psychosocial treatments such as cognitive behaviour therapy¹ and interpersonal psychotherapy are effective in mild to moderate paediatric depression. However, effectiveness in severe depression (when symptoms

are serious and last more than six weeks in at least two of three contexts – home, school, peers) is questionable.² This raises the question of drug treatment.

Tricyclic antidepressants are not more effective than placebo in children and adolescents.³ They are cardiotoxic, particularly in overdose, and are therefore not recommended. A meta-analysis of data from published and unpublished randomised controlled