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 SSRIs 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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(See **'Suicide and antidepressants in children')**

Key words: depression, cognitive behaviour therapy, fluoxetine, paroxetine.

(Aust Prescr 2005;28:111–13)

Controlled trials show that psychosocial treatments such as cognitive behaviour therapy[1] 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

trials (practically all company-sponsored) that evaluated a selective serotonin reuptake inhibitor (SSRI) versus placebo in patients aged 5–18 years concluded that only fluoxetine had evidence of effectiveness.[4] A recent randomised trial funded by the US National Institute of Mental Health also showed response rates were higher with fluoxetine (61%) than placebo (35%) or cognitive behaviour therapy (43%) in severely depressed adolescents when global clinical improvement was considered. Combined fluoxetine and cognitive behaviour therapy worked best (71%).[2]

SSRIs are less toxic and have fewer unwanted effects than tricyclic antidepressants, but it has been suggested that, paradoxically, SSRIs may induce suicidal behaviour in the young. Ascertaining whether this is true is not easy because depression also increases the risk of suicide. So far, data are contradictory. On the one hand, pharmacoepidemiological and ecological studies suggest that increased use of SSRIs may have resulted in a reduction in youth suicide and that SSRIs are not found more often than expected in young suicide victims. On the other hand, a review[5] by the US Food and Drug Administration of 24 controlled trials involving more than 4400 children and adolescents showed a robust if small (2%) short-term increase in the incidence of suicidality (suicidal thoughts, attempts) in those receiving antidepressants, mostly SSRIs, compared with placebo. There were no suicides. The mechanisms underlying increased suicidality are unclear. SSRIs, particularly paroxetine[5], can induce akathisia, agitation and irritability (so-called 'activation'). Symptoms of 'activation' may be an indicator of increased suicide risk. Like other antidepressants, SSRIs can also trigger manic switches.

This is a rapidly evolving field in which new data are becoming available all the time and clinicians need to change their practice accordingly, considering that the balance between benefit and harm is neither simple nor static. Conclusions derived from clinical trials may not apply to individual patients for methodological, genetic, physiological, psychosocial and cultural reasons. Also, the weight given to the evidence may vary in line with changes in personal and social values. Electroconvulsive therapy is a case in point.[6] (Ironically, electroconvulsive therapy could become an increasingly attractive treatment option for youth depression due to concerns about antidepressants.) Hence, clinical practice should be guided by a careful appraisal of benefit and harm based on best evidence, clinical experience, and the needs, circumstances and wishes of each individual patient.

SSRIs have been widely used 'off-label' from the early 1990s, but none is formally approved for paediatric depression in Australia. The data about effectiveness are not great. The risks are small, but real. Conversely, depression is a serious illness that produces much personal suffering and can lead to social problems, poor physical health and suicide. Given a high recurrence rate, the effects of depression can be particularly harmful during childhood and adolescence, the stage when personality, professional and social skills are developed. Yet, youth depression is often ignored, not diagnosed, and not treated. For example, an Australian national household survey showed that of all depressed adolescents, 11% had seen a GP or paediatrician, 17% had used mental health services, and only 3% had been prescribed antidepressants.[7] The current evidence suggests that psychosocial treatments, not medication, should be used in mild and moderate depression, but they are no panacea.[2] Delivering them can pose challenges because clinicians may lack skills and confidence in using these therapies. Psychosocial treatments may also be unavailable in public sector services or be difficult to access because of cost, long waiting lists, or lack of services (for example, in rural areas). Further, depressed young people may be more reluctant to become engaged in these treatments because of anger, lack of motivation or insight, and demoralisation. Fluoxetine has a place in the treatment of severe depression in the young.[2,4] Fluoxetine and cognitive behaviour therapy should be the preferred option because the combination may be more effective and may reduce suicidal risk.[2]

When treatment with SSRIs is begun, the patients (and their families when appropriate – for example in younger adolescents) must be informed of the risk of increased suicidal thoughts and attempts, and adverse effects, so that they can detect 'activation', a manic switch, or an increase in suicidality, as well as discussing practical ways of dealing with them and enhancing patients' safety. This may require a reduction of the dose, because the adverse effects are dose-related. It is imperative to review patients often and monitor them closely for adverse effects, particularly during the first few weeks of treatment.

The Royal Australian and New Zealand College of Psychiatrists, the Royal Australasian College of Physicians and the Royal Australian College of General Practitioners have recently issued a statement about the use of antidepressants in children. This provides further guidance about the prescription of these drugs.[8]

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Further reading

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Professor Rey was a member of the advisory committees for atomoxetine (Eli Lilly) and methylphenidate (Janssen-Cilag) and was funded by Eli Lilly to attend an international conference.

Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Varicella vaccine

Editor, – Despite the risks, the article 'Frequently asked questions about varicella vaccine' (Aust Prescr 2005;28:2–5) recommends widescale immunisation. There are three arguments against this strategy. Firstly, vaccine immunity may wane over time leaving susceptible adults. Secondly, immunising part of the population may shift the disease burden to those who are not vaccinated and because they will be less likely to acquire chickenpox in childhood they risk more severe disease in adulthood. Thirdly, the effect of vaccination on the incidence of herpes zoster is unknown.

The data so far show that chickenpox in immunised individuals is less severe. However, it is too early to know how this will change as immunised infants reach adulthood.

In 2000 mathematical modelling showed that immunising 90% of infants would produce an initial 'honeymoon' period of low incidence, one or more post-honeymoon epidemics in adolescents and young adults 10–20 years later, and an equilibrium reached after 20–40 years in which the incidence in adults is similar to that in the pre-vaccine years.[1] The evidence from the USA on reduced incidence in all age groups covers only five years of experience, which is within the honeymoon period predicted by the modelling. This is insufficient time for epidemics in adults to occur through the build-up of susceptible people, as partial population immunity increases the interepidemic interval.

The impact of varicella vaccine on herpes zoster is complex. There is reasonable evidence that adults exposed to children, or exposed to chickenpox, have less chance of developing zoster, through presumed immunologic boosting by exposure to varicella zoster virus.[2] Modelling shows that immunisation causes an increase in herpes zoster for up to 50 years until immunised infants reach old age.

Due to the infectivity of reactivated herpes zoster it is not possible to eliminate varicella zoster virus in the way measles or polio could be eliminated completely. The aim of immunisation is therefore to reduce the burden of varicella disease rather than disease elimination. Since the burden of serious disease, particularly mortality, is in adults, and the modelling shows that in the long term the incidence in adults will not be affected by even high levels of vaccination coverage, the logic of universal vaccination has to be questioned.

Vaccination undoubtedly reduces childhood disease and saves the costs of medical care, childcare costs and lost income for parents while they look after sick children. Health decisions, however, should be primarily based on health considerations rather than economics.

The current low burden of disease from varicella means that it would take only a small rise in varicella in adults for us to be worse off than we were without the vaccine.

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