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Should we prescribe antidepressants to children?

In June last year, the committee on safety of medicines (CSM) advised against the use of paroxetine in depressed children and adolescents. This was subsequently followed by a similar warning regarding the use of other selective serotonin reuptake inhibitors (SSRIs), with the exception of fluoxetine (http://www.mhra.gov.uk/). The basis of this decision was a detailed review of both the published and the unpublished data. The latter were obtained from pharmaceutical companies who had not reported negative results from clinical trials to the medical community. The addition of the pharmaceutical industry data to published results exerted dramatic effects on the efficacy of available compounds. Thus with the exception of fluoxetine, the risks outweigh the benefits of the SSRIs in the treatment of childhood depression. In particular, there is evidence of a non-significant trend towards increased suicidality with most SSRIs compared with placebo. These findings have been supported by a further recent meta-analysis of the available published and unpublished data (Whittington *et al*, 2004). A review of the safety and efficacy of antidepressants in children and adolescents by Jureidini *et al* (2004) has also criticised the quality of reporting of the published trials. The review concluded that the benefits of SSRIs have been exaggerated, including those of fluoxetine, and the adverse effects have been downplayed. The authors suggest that psychological treatments are probably safer and more effective.

In the USA, the Food and Drugs Administration (FDA) responded to these concerns by initiating its own analysis of the pharmaceutical company data. Subsequent to this review, in September 2004 the FDA published a statement concluding that there was an elevated risk of suicidality in paediatric patients treated with antidepressants, and recommended labelling with a 'black box' warning. However, unlike the CSM, the FDA did not distinguish between fluoxetin and other antidepressants and, significantly, recommended that these products not be contraindicated in the USA because access to these therapies was important for those who could benefit (http://www.fda.gov/bbs/topics/news/2004/NEW01116.html).

The American College of Neuropsychopharmacology (ACNP; http://www.acnp.org/exec_summary.pdf) published a preliminary assessment of the evidence (largely published data), which opposed the CSM conclusions, arguing that the increased risk of suicidality was not significant, and there have been no actual suicides in these trials involving several thousand children. Similarly, no increased rates of suicide have been found in adult patients taking SSRIs in analyses of over 40 000 adult depressed patients, who participated in depression treatment trials (Khan *et al*, 2003). Recent reviews of the treatment of adult depression by the CSM and the National Institute for Clinical Excellence (NICE) have likewise not found clear evidence for an excess of suicidality in patients treated with SSRIs (http://medicines.mhra.gov.uk/ourwork/monitorssafequalmed/safetymessages/SSRIfinal.pdf; www.nice.org.uk/pdf/CG023quickrefguide.pdf). Epidemiological studies have also found an association between the increased use of antidepressants in young people and a reduction in suicide rate. For example, Olfson *et al* (2003) found that a 1% increase in the use of antidepressants in adolescents was associated with a significant decrease of 0.23 suicides per 100 000 adolescents per year ($P<0.001$). This finding does not indicate a causal relationship between medication use and diminished suicidality but does suggest a need to exercise caution about published negative associations.

The CSM findings have generated a great deal of controversy and media interest worldwide. What are clinicians and the public to make of this current controversy, and how should depression in young people now be treated? Several facts need to be considered when deciding on the most suitable treatment for childhood depression. First, prepubertal childhood depression is not aetiologically the same as adolescent depression even though the disorders show similar clinical presentations (Kaufman *et al*, 2001; Silberg *et al*, 2001*a*; Birmaher *et al*, 2004). The disorder is relatively uncommon in prepubertal children, but prevalence rises sharply in adolescence (Meltzer *et al*, 2000). There is evidence that shared environmental factors are important in both child and adolescent onsets whereas genetic factors are only important in adolescent depression (Rice *et al*, 2002). Therefore, it is likely that the treatment needs of children and adolescents are different. Second, depression in young people has a multifactorial aetiology (Silberg *et al*, 2001*b*) and is highly comorbid (Angold *et al*, 1999). To expect large single treatment effects in such a clinically heterogeneous condition is unrealistic. Efficacious

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treatment is most likely to be multimodal with a focus on non-depressive as well as depressive features. Third, adolescent onset major depression shares more similarities with adult depression. Adolescent forms develop a protracted course into adulthood with increased suicidality and adverse psychosocial consequences (Fombonne *et al*, 2001*a*,*b*). They are also more likely to show evening cortisol hypersecretion than child forms (Solokov & Kutcher, 2001). Affective disorder is the most common psychiatric disorder in adolescence associated with both suicidal behaviour and completed suicide (Shaffer *et al*, 1996; Meltzer *et al*, 2001).

The differences in natural history of pathophysiology between child and adolescent onset depression detailed above need to be considered when reviewing the current available evidence for the treatment of depression. The aforementioned literature suggests that biological treatments may be more relevant to postpubertal adolescents. With regards to the issue of efficacy of SSRIs, as yet there has been no systematic review of the developmental (age or puberty) effects on treatment outcomes, and therefore it is unclear whether children and adolescents respond differently to medication. From a clinical perspective 'pure' depression is an uncommon occurrence, however cases with non-depressive comorbid disorders are excluded from medication treatment trials or the impact of non-depressive symptoms on outcome measures are ignored. Thus the efficacy of antidepressants in a typical depressed clinical population on overall well-being and levels of psychosocial impairment is poorly documented. Although effects may be small on reduction of depression symptoms they may have a substantial bearing on functional outcomes such as social and educational performance.

The issue of suicidality is complex, and the trend towards an increase in suicidal behaviour with SSRIs is clearly worrying. However, there is much uncertainty regarding the measurement of suicidality within the drug trials, as no standardised methods of measurement were developed for these studies (http://www.fda.gov/cder/drug/antidepressants/classificationProject.htm). In addition, suicidal children were frequently excluded from participating in the trials. Since suicidality is considered to be a core concept in depressive disorder, it can be argued that these studies have been unable to examine the effects of medication on the most severely affected young people. This population includes those most likely to be recipients of medication in specialist child and adolescent mental health services in the UK. In a recent British epidemiological survey, 41.2% of children with depression, between the ages of 11 and 15 years had tried to harm, hurt or kill themselves (Meltzer *et al*, 2001). This implies that nearly half of young people with major depression would be excluded from treatment trials. These are the very children who are most in need of treatment, and so it is imperative that they can be included in studies of the treatment of depression. The randomised controlled trials (RCTs) published to date are therefore potentially flawed at the level of population ascertainment. Given that seriously depressed young people with and without suicidality need treatment, what are the current available therapeutic options to child mental health specialists?

Should we use the tricyclic antidepressants?

Tricyclic antidepressants (TCAs) have not been contra-indicated in juvenile depression and are known to be effective in adults. However, a recent systematic review found no benefit of TCAs in children and only very modest effects in adolescents (Hazell *et al*, 2003). TCAs are known to have an adverse side-effect profile and are toxic in overdose (Cheeta *et al*, 2004), and therefore the risk of prescribing TCAs outweighs the possible benefits in depressed children and adolescents, who are known to have a high rate of suicidal behaviour.

What about psychotherapy?

Cognitive–behavioural therapy (CBT) is the best studied psychological therapy in childhood depression, and has been shown to be effective in mild to moderate depression (Harrington *et al*, 1998). However, it has been studied less often in moderate to severe depression. Clarke *et al* (2002) recruited 88 depressed adolescent offspring of depressed parents, and failed to find any additional benefits of CBT over usual care, which generally included the prescription of psychotropic medication. More recently, a large, multicentre RCT in the USA randomised 439 subjects to one of four treatment options: fluoxetine alone, CBT alone, combined treatment and no treatment (control group). The findings showed a clear advantage of combined treatment over medication alone in the treatment of adolescents with depression. However, although there was evidence of the benefits of fluoxetine over no treatment, there was no treatment effect for CBT compared with placebo controls (March *et al*, 2004). Fluoxetine alone was associated with more adverse events, including a small number of harm-related adverse events, although not suicidal thinking. Interestingly, the addition of CBT seemed to be protective against harm-related behaviours. The authors point out, however, that there were only seven attempts at self-harm in the first 12 weeks of the study and so the potential positive effects of CBT on harm reduction require confirmation. This new evidence is substantial and suggests that combining CBT and fluoxetine is the treatment of choice in moderate to severe adolescent depression, but prescribing fluoxetine alone may be acceptable in cases of concern and where adjunctive psychological treatment is not available. In contrast, CBT alone does not seem to be efficacious in this group. These results need replication and more detailed information on the incidence of adverse events and the impact of comorbidities on treatment efficacy is also required.

Interpersonal therapy (IPT) has also been studied, albeit less often (e.g. Mufson *et al*, 2004), but treatment trials of the size and nature described above are lacking. Until IPT has been studied in comparison with other treatments of known efficacy it is difficult to be clear about its role in the treatment of young people with

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depression. The early studies of IPT in community health settings are promising and this treatment deserves further systematic investigation.

Although the adverse effects of medication are regularly examined in treatment studies, there is no tradition of reporting any potential adverse effects of psychological treatments. Psychological treatments may have negative effects. For example, Dishion & Andrews (1995) found that a group intervention for boys with behaviour difficulties caused an increase in conduct problems. Psychological therapy can be time-consuming and intrusive, and until potential averse effects are routinely measured, we should be more guarded about their risk–benefit balance and perhaps inform patients and their families that side-effects are not known rather than do not occur. Future studies should include a cost–benefit analysis when comparing the relative values of two (psychological and/or pharmacological) treatments. CBT is expensive in the short-term, not only in terms of therapist time, but also in terms of the costs incurred by the patient and family in attending sessions, which are generally more frequent than required with medication. It is possible that short-term costs may be offset by longer-term gains, but as yet we do not have this type of analysis available to us.

Treatment pathway

Childhood depression is a heterogenous condition, with a multifactorial aetiology, and requires a multimodal treatment approach. Medication is not usually the first-line treatment, and many cases will resolve following a simple psychoeducational approach with basic interventions, such as liaison with other relevant agencies. If the depression persists and is relatively mild, then CBT should be tried. However, if the depression persists and is more severe, then fluoxetine should be considered together with CBT. If an adequate trial of fluoxetine and CBT has been given without any response, then the diagnosis, and psychosocial factors need to be reviewed. If all else fails, an alternative SSRI may have to be considered, in consultation with other child psychiatry colleagues. Sertraline and citalopram appear to be the most likely choice of second-line medications. The risk–benefits of prescribing an alternative SSRI will then need to be reviewed in each individual case and explained to the carers and adolescents.

Future research

Clearly we need more trials of SSRIs in young people with moderate to severe depressive illness which do not exclude subjects with comorbidity and suicidality. Trials need to examine factors which may predict response to treatment, such as age and severity, and adverse effects need to be monitored systematically, in particular, suicidality. Likewise, we need more studies of psychological treatment in severely depressed adolescents, and adverse effects also need to be examined. Finally, in view of the recent scandal regarding the non-publication of trial data, mandatory trial registration and publication of results is essential in order for clinicians, parents and adolescents to be able to make informed decisions about the safest and most appropriate treatment for children in what is a distressing and disabling condition.

Declaration of interest

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