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Facing the evidence: antidepressant treatment in children and adolescents

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Depression in childhood and adolescence is a challenging problem for those affected, their parents and their physicians. Before reaching the age of 18, about 1 in 5 young people will experience an episode of major depressive disorder, an illness that is characterized by a high recurrence rate, persistent psychosocial impairment and increased risk of suicide. Disappointed by the ineffectiveness and potential toxicity of tricyclic antidepressants,[1] physicians welcomed practice guidelines in the late 1990s that suggested the newer selective serotonin reuptake inhibitors (SSRIs) were effective and better tolerated.[2] The prescribing rate for antidepressants, particularly SSRIs, in young people has increased steadily in the past decade.[3]

However, 2003 brought surprises for both researchers and treating physicians. In light of the results of several large randomized controlled trials, regulatory agencies in the United Kingdom, the United States and Canada declared that paroxetine was contraindicated in the treatment of major depressive disorder in patients under 18 years of age. These trials had shown paroxetine to be ineffective and to be associated with double the rate of suicidality and aggression compared to placebo.[4] Next, 3 trials of venlafaxine therapy for pediatric depression found this SSRI also to be ineffective, and to be associated with double the rate of suicidality and hostility compared to placebo.[5] A general advisory was then issued regarding the increased risk of suicide in pediatric use of *all* SSRIs.[6,7] These developments not only raise new concerns about the presumed effectiveness and safety of SSRIs for young people, but also pose disturbing questions about publication bias and the questionable interpretation of research data on the treatment of childhood depression.

It is important to recognize that the SSRI therapy for young people with depression is characterized by high placebo response rates.[1] Twelve small double-blinded controlled studies published by the mid-1990s demonstrated no effect of tricyclic antidepressants or fluoxetine compared to placebo in childhood and adolescent depression, and a placebo response rate of 40%–60%. Pharmaceutical companies, perhaps encouraged by patent extension legislation in the late 1990s, undertook larger trials with the hope that greater statistical power, careful patient selection, higher doses and a longer duration of treatment (8–10 weeks) would yield more favourable results. The few trials published to date show minimal effects that, from a clinical standpoint, are trivial. For example, the recent sertraline study[8] involving almost 400 patients from 2 pooled trials demonstrated borderline statistical significance on selected measures of improvement, but these did not include remission, the most clinically important outcome. Sixty-nine percent of patients improved on medication, versus 59% on placebo. Essentially, only 1 in 10 patients receiving sertraline improved, a result described in the report as "statistically and clinically significant" when it is almost certainly clinically meaningless. The term "statistical power" implies that a large trial is inherently better than a smaller one. However, a clinically significant response should be evident in a small trial; a large trial is needed only to detect very small effects, which may or may not be clinically meaningful.

Fluoxetine is the only antidepressant that has received

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formal approval in children, but the evidence of efficacy in the 2 published trials of this drug is weak. In the trial that showed the most significant results, patients were carefully selected to reduce placebo responders through a 3-week baseline observation period followed by a 1-week placebo trial to remove patients who improve quickly with supportive attention or placebo, and through exclusion of those at risk of bipolar disorder.[9] Fluoxetine showed an effect on selected measures of clinician-rated improvement, but there was no increase in rates of remission or recovery, and no difference in the patients' self-rating of depression, the parents' ratings, global psychiatric symptoms or global functioning. As described in an independent statistical analysis of the fluoxetine trials,[10] this trial failed with respect to both of its predetermined primary outcome measures. Furthermore, the reanalysis revealed an uneven allocation of patients with comorbid anxiety to receive fluoxetine. In the absence of anxiety disorder, there was no superiority of the medication over placebo.

Why was it left to regulatory bodies to publicize the lack of effectiveness of paroxetine and venlafaxine? The single published placebo controlled trial concluded that paroxetine was effective and safe in adolescent depression.[11] But none of the large negative trials (2 each for paroxetine and venlafaxine) were published, a phenomenon that undermines evidence-based medicine.[12] Pharmaceutical companies seeking regulatory approval are obliged to make the results of all clinical trials they sponsor available to regulatory agencies. However, there is no requirement for these results to be published or even made available to investigators.[13] Those researchers, including myself, who *did* see results of negative paroxetine industry trials were prohibited by nondisclosure contracts from discussing them.

In addition to their weak or nonexistent evidence of efficacy, SSRIs may have serious adverse effects in children. Although rates of suicidal ideation and suicide attempts are low in the SSRI trials reviewed by regulatory agencies (2%–5%),[4,5] observations in clinical trials and case reports indicate that up to 25% of children placed on SSRIs for any disorder will experience other psychiatric adverse effects including agitation, irritability and behavioural disinhibition.[14] In the adolescent paroxetine trial,[11] 10.5% of patients discontinued paroxetine because of "serious" psychiatric adverse effects, of which the most common was euphemistically described as "emotional lability," further defined as "suicidal ideation/gestures; conduct problems or hostility, e.g., aggressiveness…". Such responses led 7.5% of the outpatient participants prescribed paroxetine who initially were only mildly depressed to be admitted to hospital, while none of the placebo group required hospital admission. The authors dismissed this result by stating that these psychiatric adverse effects were not attributed to the medication — despite the fact that numerous reports of agitation and suicidal behaviour in young people treated with SSRIs have accumulated since the 1990s.

The fact that researchers have minimized these adverse events underscores concerns about the complex conflicts of interest that may affect the conduct, analysis and reporting of clinical trials.[12,13] The sertraline trial, in which our site participated, did not include a side-effect checklist in the protocol, yet the medication was described as well tolerated. With only 1 in 10 patients responding to medication, almost 1 in 10 discontinued it because of a serious adverse effect. Such effects included suicidality, the occurrence of which doubled in the treatment group compared to placebo.[8]

The high placebo response of SSRIs may reinforce physician prescribing, and it has been difficult for many physicians to accept that SSRIs may be ineffective. A complicating factor is that the public at large has now accepted the model of depression as a chemical imbalance for which medication is the treatment of choice, and physicians may experience pressure to prescribe. The disappointing reality is that antidepressant medications have minimal to no effectiveness in childhood depression beyond a placebo effect. They do appear to be more effective in anxiety disorders and obsessive–compulsive disorder, but there are also unpublished negative trials for these indications.[4,5]

The physician treating a child or adolescent with recent onset of depression is advised to begin with education regarding sleep hygiene, exercise, practical coping skills and family interventions, and to provide the frequent, supportive contact typical of clinical trials. Although there is evidence for the effectiveness of cognitive behavioural therapy and, possibly, interpersonal therapy, discussion of psychosocial treatments is beyond the scope of this commentary.

After a period of careful observation and a trial of nonpharmacological therapies, children with persistent and severe depression or comorbid anxiety disorders may need to be treated with medications. In this situation physicians could choose an SSRI that has been approved for use in children and adolescents, such as fluoxetine for depression or sertraline for obsessive–compulsive disorder. Physicians need to be alert to the fact that the psychiatric adverse effects of SSRIs overlap with manifestations of depression itself; without this realization, physicians may make the mistake of increasing rather than decreasing the SSRI dose of children experiencing these adverse effects, or of unnecessarily prescribing adjunctive mood stabilizers and atypical neuroleptics. On the other hand, if the SSRI is discontinued, assessment may be further complicated by the emotional and behavioural discontinuation effects of withdrawing the drug. Physicians should inform young patients and their parents that medication will not cure depression, but might improve some depressive symptoms. Families must also be informed that psychiatric or behavioural adverse effects are at least as likely as antidepressant effects.

It is clear that our efforts to establish a scientific basis for the treatment of childhood depression are severely compromised by both unpublished research and the uncritical acceptance of published data. It is disturbing to note that there has been no formal response to this crisis from opinion leaders in

child psychiatry, many of whom were investigators in both published and unpublished trials.

Fortunately, drug regulatory agencies are now forcing us to face the evidence. As the year ended, the British regulatory agency, the Medicines and Healthcare products Regulatory Agency, announced unacceptable risk–benefit profiles for all antidepressants except fluoxetine for the treatment of major depressive disorder in children under 18.[15] Their independent reanalysis of the sertraline trials data[8] yielded 2 negative trials, as predicted. Publication of all clinical trial results and systematic ascertainment of adverse effects must become research standards. Furthermore, data must be subject to analysis by independent experts who are alert to conflicts of interest that may distort the interpretation of data. Practice guidelines need to be rewritten to reflect a critical analysis of the full body of evidence, both published and unpublished.

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