Antidepressants and suicide in children and adolescents: a storm in a teacup?

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Paediatric psychopharmacology has entered a new and exciting era, with a substantial increase in the number of randomised controlled trials in paediatric mood and anxiety disorders. Although not a child and adolescent psychiatrist, I have followed the recent controversies and negative press surrounding antidepressants and self-harming behaviours in youth with keen interest, particularly given the manner in which regulatory authorities have taken stock of the available evidence to answer the deceptively simple question: 'Are antidepressants associated with increased suicidality?'

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Why is this an issue now?

The idea of SSRI (selective serotonin reuptake inhibitor)-associated suicidality first came to light in the early 1990s, yet despite more than a decade of study this critical question has yet to be answered definitively. The issue appears to have erupted again on 10 June 2003 when the British Medicines and Healthcare Products Regulatory Agency (MHRA) issued a press release prohibiting the use of paroxetine in children and adolescents under the age of 18. Their decision was based on a review of unpublished data submitted by GlaxoSmithKline. Upon analysis of data from three trials of paroxetine in paediatric depression, all of which were negative, it emerged that paroxetine was associated with a two- to threefold higher rate of self-harm and suicidal behaviour than placebo. The MHRA also reported that suicidality appeared to be a significant risk with all antidepressants that were assessed, other than fluoxetine. In contrast to other SSRIs, data from three clinical trials submitted on the use of fluoxetine in paediatric depression indicated that there was no increased risk of suicide-related events or attempted suicide.

About a week later, the US Food and Drug Administration (FDA) issued a weaker warning noting the controversy and advising dose monitoring because of the possible increased risk of suicide. The FDA did, however, point out that of the more than 4 000 children and adolescents who had participated in these studies, *none* had actually committed suicide. Furthermore, it was clear from the data submitted that adverse events suggestive of suicidality (broadly taken to include ideation, self-harm, suicide attempts) had been captured and coded differently by different trial sponsors and that assessment of suicidality had been largely elicited through basic, unstructured inquiry or a single item on a depression rating scale.

Suicide warnings

A contentious and emotional public advisory committee meeting on the risk of treatment-emergent self-harming behaviours associated with SSRI use in children and adolescents followed, after which the FDA requested on 22 March 2004 that manufacturers of 10 antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline,

escitalopram, venlafaxine, bupropion, nefazodone, mirtazapine) incorporate more stringent warnings of suicide risk in their package labelling that would apply to both paediatric and adult usage. The new label warning states that 'anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania have been reported in adult and paediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.'

Mechanisms of suicidality and SSRIs

There are three possible mechanisms by which these medications may potentially precipitate suicidality. First, behavioural activation/disinhibition induced by the SSRIs may make latent suicidal thoughts more explicit and patients may be inclined to act on them when activated/disinhibited. Second, akathisia or intense restlessness, a rare side-effect associated with SSRIs, may be so disturbing for some patients that they may consider suicide rather than endure the uncontrollable restless feelings. Akathisia is a side-effect that patients can be warned about and that clinicians can look for closely and treat with adjunctive medication, if needed. The third mechanism may be the natural history of recovery from depression, which when treated effectively is usually associated with a resolution of physical symptoms (lack of energy, sleep and appetite disturbances) first, before any observable improvement in subjective depressed mood. As energy levels begin to recover in the first week or two of starting medication, the risk of suicide may increase in patients who previously lacked the energy or motivation to attempt it.

Benefits versus risks

Antidepressants in general, and SSRIs in particular, have had a tremendous impact in reducing the burden of depression and improving the quality of life of children and adolescents, and clinical experience and intuition would suggest that they reduce rather than increase suicidality. A study in the USA that examined this relationship found that an increase in adolescent antidepressant use over the past decade (1990 - 2000) was, in fact, associated with an overall decrease in completed suicides.[1] To date, several SSRIs have undergone rigorous testing in double-blind, placebo-controlled, short-term studies of efficacy and safety. Fluoxetine has been approved by the FDA for the treatment of children and adolescents with major depression. Recent meta-analysis of published and unpublished trial data supports findings that fluoxetine has a favourable risk-benefit profile for the treatment of depression in children and adolescents.[2]

Fluoxetine, sertraline and fluvoxamine have FDA approval for the treatment of childhood obsessive-compulsive disorder. Fluvoxamine and fluoxetine have also demonstrated efficacy for generalised anxiety disorder, separation anxiety disorder, and social phobia but do not have FDA indications for these disorders in youth.[3,4] In contrast to the tricyclics, which have been associated with lethality in overdose and sudden unexplained deaths, the SSRIs are associated with very few serious side-effects and are considerably safer in overdose. That said, SSRIs have been associated with problematic side-effects such as behavioural activation/disinhibition and akathisia. While these side-effects are not unique to youth, prepubertal children are arguably more sensitive to the dose-dependent activating effects of the SSRIs early on in treatment.[5]

Summary

So have the regulatory authorities overstated the risks and underestimated the benefits of antidepressants in the treatment of depression in youth? Considering that existing data from clinical trials on suicidality appear contradictory and incomplete, more careful scrutiny of the risks and benefits is clearly needed. Better data and a cleaner, more systematic approach toward adverse event data reporting may be able to answer the question at hand. Risk benefit analyses in paediatric trials may be more complicated because of high placebo response rates which make it difficult to show statistically *and* clinically significant drug-placebo differences. For example, in two recent randomised controlled trials of sertraline in children and adolescents (aged 6 - 17) with *DSM-IV* defined major depressive disorder, undertaken at the request of the FDA, 69% of those who were taking sertraline were classified as responders compared with 59% of patients

taking placebo.[6] While these differences were statistically significant, the mean change in scores from baseline to endpoint on the primary outcome measure, the Children's Depression Rating Scale-Revised, between the groups was so small so as to be of minimal clinical significance. In addition to high placebo response rates, other problems include non-publication of negative findings, withholding of unfavourable data and under-reporting of adverse events.[2]

For now, monitoring child, adolescent, and adult patients closely for suicidal ideation during the first weeks of antidepressant therapy and during dose titrations of their medication should always be part of the armamentarium and standard of care of any good clinician.

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