Editorial

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Should we use antidepressants for the treatment of major depressive disorder in children and adolescents?

Deve-se utilizar antidepressivos no tratamento de depressão maior em crianças e adolescentes?

Major depressive disorder (MDD) affects 2% of children and 4% to 8% of adolescents.[1] MDD is associated with in school performance and social relationships, comorbid substance abuse, and an increased risk of suicide attempts. Pediatric MDD is a recurrent illness that usually continues into adult life. Therefore, it is important to have efficacious short and long-term treatments for both the acute management and the prevention of recurrences of this potentially life-long disorder.

Selective Serotonin Reuptake Inhibitors (SSRIs) are one of the current treatments available for pediatric MDD. Recently, questions have been raised regarding their efficacy and safety in for the treatment of children and adolescents. Fluoxetine is the only SSRI approved thus far by the U.S Federal Drug Administration (FDA) for the treatment of pediatric MDD, based on consistent positive results in more than one study. In three studies of fluoxetine, two of sertraline (combined into one), and one each of citalopram and paroxetine, the proportion showing clinically significant improvement was significantly greater in medication (50-60%) than in placebo (30-50%), with the number of subjects needed to treat to observe one improvement (NNT) ranging from 4-10. A smaller proportion (30-40%) of subjects in these studies achieved full symptomatic remission,[2-3] indicating that the optimal treatment for pediatric depression may involve a higher dose, a longer duration of treatment, or augmentation with other pharmacological or psychosocial treatments.[4]

Four unpublished, industry-sponsored studies with SSRIs (citalopram, escitalopram, and two with paroxetine) did not find differences between active medication and placebo. In these studies, subjects responded to both SSRIs and placebo, suggesting that these studies may have included subjects with mild depression, or even other methodological bias. For example, the greater the numbers of sites, the more challenging are the issues of quality control, and indeed, the drug-placebo difference is inversely proportional to the number of sites. Also, studies that included a placebo washout phase, a more stringent definition of MDD, and those conducted by academic centers showed larger differences between antidepressants and placebo.[4]

A few unpublished, industry-sponsored randomized controlled trials (RCTs) have evaluated the effects of other classes of antidepressants for the treatment of depressed youth. Nefazodone was significantly better than placebo for youth with MDD, but the concern about hepatotoxicity have limited its use. Two RCTs with venlafaxine and two with mirtazepine were also negative. However, a reanalysis of the venlafaxine trials showed significant effects over placebo for adolescents, but not for children. No RCTs have been conducted in pediatric MDD with bupropion, although open trials are promising.

Despite recent concern about SSRIs in pediatric populations, SSRIs have been well tolerated by both children and adolescents with few short-term side effects (e.g., gastrointestinal, headaches), although the long-term side effects of SSRIs have not been systematically evaluated. Approximately 3-8% of children and adolescents taking SSRIs for the treatment of depression or anxiety disorders develop increased impulsivity,

agitation, irritability silliness, or "behavioral activation". These symptoms need to be differentiated from mania or hypomania that may appear in children and adolescents with bipolar disorder predisposition.

Analyses conducted by the British Medical Healthcare Product Regulatory Agency (MHRA) and the FDA on all available pediatric RCTs show a 1.8-fold increased risk of suicidality (new-onset or worsening suicidal ideation or behavior) in drug compared to placebo (see the MHRA and FDA websites), meaning on average a rate of suicidality of 4% in drug and 2% in placebo. Relatively few attempts and no suicides in trials of 4300 subjects were reported.

The MHRA concluded that all SSRIs other than fluoxetine were contraindicated for pediatric depression. The FDA issued a "black box" warning to alert clinicians to the risk of suicidality, while still allowing their use. The FDA analysis of the Treatment of Adolescent Depression Study (TADS) clinical trial helps to put the risks and benefits of SSRIs in perspective. Fluoxetine, compared to placebo, had a 4.6-fold increased rate of suicide-related adverse events, with a number of subjects needed to observe one side effect or harm (NNH) of 14. However, in intent to treat analyses, fluoxetine was associated with a significant decrease in suicidal ideation compared to placebo, as well as a *significantly* higher rate of clinical improvement in depression relative to placebo (NNT = 4). Thus, nearly 4 times as many youth showed improvement in depression as developed suicidal adverse events, which appears to be an acceptable risk-benefit ratio.

Despite the findings from the FDA analyses, it seems unlikely that SSRIs pose a serious increased risk for adolescent suicide. Youth suicide rates in the United States and in other countries have been *declining* for almost a decade, while SSRI prescriptions for adolescents have increased dramatically.[5-6]

In summary, there is a small, but *increased* risk of suicide-related adverse events associated with SSRI use in children and adolescents, which must be balanced against SSRI-related improvements in suicidal ideation and depression. Unfortunately, the FDA analyses do not shed light on the characteristics of the 4% of youth exposed to SSRIs most likely to become suicidal. Further studies are indicated to identify the extent, precursors, and mechanisms of increased suicidality associated with SSRI treatment. Clinicians and investigators have suggested that this effect may be attributable to induction of agitation, disinhibition, a mixed state, non-compliance resulting in non-response, withdrawal symptoms, slow metabolism, variations in genetic polymorphisms that increase the susceptibility to side effects, or a bipolar diathesis.

To date, there is strong data showing that fluoxetine is efficacious for the acute treatment of depressed youth, with positive, but less unequivocal support for the efficacy of sertraline and citalopram. However, since some children and adolescents do not completely respond to SSRIs, combination with cognitive behavior therapy or interpersonal psychotherapy is recommended. Physicians considering using SSRIs must explain to parents and patients the benefits and risks associated with of antidepressants and alternative, non-medical treatments and together make the final decision taking into account the negative psychosocial consequences and increased risk for suicide attempts and completions associated with untreated MDD.[7]

Boris Birmaher, David Brent
University of Pittsburgh Medical Center
Western Psychiatric Institute and Clinic

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