

**Selective serotonin
reuptake inhibitors in
children and adolescents
with major depression**

**Inibidores seletivos da
recaptação de serotonina
em crianças e
adolescentes com
depressão maior**

The selective serotonin reuptake inhibitors (SSRIs) entered the world wide market place in the late 1980s with the introduction of fluoxetine. Since then five others: sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram have also become available in many countries around the world. These compounds are used to treat major depression, obsessive-compulsive disorder, generalized anxiety disorder, panic disorder and social anxiety disorder. Due to the perceived safety of these drugs and their convenience (e.g., single day dosing, no need for blood level monitoring), the SSRIs have dominated the market. Although a majority of the research to date has been in adult populations, there have been several large scale studies in pediatric populations. Thus, in many western countries, one or more of the SSRIs are approved for obsessive-compulsive disorder (OCD) or depression in children and adolescents. Recent warnings about suicidal thoughts and self-injurious behavior in youth treated with selective serotonin reuptake inhibitors raise fundamental questions about the risk-benefit ratio of this class of medications. This paper examines this controversy and provides essential clinical considerations.

The recent controversy about the use of the SSRIs in children emerged about two years ago following a review by the British drug regulatory agency of paroxetine for depression. This agency expressed concern that the rate of suicidal ideation and behavior was greater for paroxetine-treated subjects than the rate in the placebo group. In addition, the agency concluded that the evidence for efficacy of the treatment of youth with depression was not convincing. This review was followed by a thorough examination of the evidence by the Food and Drug Administration (FDA) in the United States. Based on a meta-analysis of 24 placebo-controlled trials of the SSRIs (most of which were unpublished) involving over 4000 pediatric patients, the agency expressed concern about the possibility of worsening depression, the emergence of suicidal thoughts and behaviors, hyperactivity, irritability, and impulsiveness following the initiation of SSRI treatment. Thus, in October, 2004, the FDA issued a warning on the use of SSRIs in pediatric patients (see <http://www.fda.gov/cder/drug/antidepressants/SSRIlabeling>).

Concern about the suicidal ideation and hyperactivity in young people treated with SSRIs is not new. The combination of hyperactivity, elevated mood and impulsiveness, often labeled behavioral activation, tends to occur early in the treatment and is not unique to the treatment of youth with depression. For example, in the placebo-controlled trial of sertraline in children with OCD, 13% of the subjects in the active treatment group became activated compared to 2% in the placebo group.¹ Similarly, 12.3% of children in the fluvoxamine trial showed behavioral activation compared to 3.2% for those on placebo.² It has been argued, though the evidence is unconvincing, that behavioral activation reflects an underlying bipolar vulnerability. On the other hand, activation may be an adverse effect of the drug on the developing brain. This uncertainty raises fundamental doubt about the routine use of a mood stabilizer based on the assumption that activation or hypomania signals the onset of bipolar disorder.³

Over the past decade, there have been several placebo-controlled trials with an SSRI in children and adolescents with depression.⁴ The three studies that evaluated fluoxetine showed clear superiority of the active drug to placebo.⁴⁻⁵ By contrast, in the study of paroxetine, the active drug was no better than placebo on the primary outcome measure. Similarly, the sertraline trial involving 376 youth between the ages of 6-17 years with major depression showed a statistically significant – but quite modest difference between active drug and placebo (47% improvement in symptom severity for active compared to a 40% for placebo).⁶ Citalopram also showed a modest clinical difference compared to placebo.⁷

This controversy on the use of SSRIs in children, reminds us that all treatments involve a risk-benefit equation. Given the modest benefit of the SSRIs in children and adolescents with depression and the potential for adverse behavioral effects, SSRI treatment in pediatric populations warrants careful monitoring. Appropriate treatment of children and adolescents with depression begins with a careful assessment including diagnosis, response to previous medication trials, the presence of suicidal ideation and plan, and usual sleep and activity level. Symptom severity at baseline is also essential for the detection of change over time. This can be accomplished through the use of rating scales such as the Children's Depression Rating Scale.^{5,7} Pediatric patients treated with an SSRI should be seen weekly for the first 4 weeks, bi-weekly during months two and three, and then monthly for the next few months. Furthermore, patients and families should be educated regarding potential adverse effects (agitation, irritability, unusual changes in behavior, suicidal ideation or self-injurious behavior) and instructed to report symptoms immediately to their health care provider (see http://www.fda.gov/cder/drug/antidepressants/Q&A_antidepressants.htm).

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