Current Controversies Regarding the Use of SSRIs with Children

John C. Courtney, Psy.D., MSCP, ABPdN
Child Development and Psychological Health Center, South Bend

A considerable amount has been written about the use of antidepressants with children in the last 18 months, particularly regarding the potential suicide risks posed by the administration of Selective Seratonin Reuptake Inhibitors (SSRI). Much controversy revolves around this issue. Some researchers, clinicians and families are calling for the removal of these drugs from the market, while others suggest that the warning bells being sounded are much ado about nothing.

Where is all of this noise coming from? Well, in short, Great Britain has its own form of the FDA called the CSM. In 2003, the CSM banned the use of ALL SSRIs, except fluoxetine (Prozac), with children being treated for depression. The CSM took this very controversial step because of several reports of increased suicidal and/or increased irrational and hostile behavior on the part of children taking these medications. The treatments that concerned the CSM were not limited to one particularly SSRI, however only fluoxetine had sufficient research from the CSM's perspective to support its continued use in children.

The result of the CSM's decision prompted 2 groups, independent of any pharmaceutical company or governmental contracts, to review post-hoc data from two randomized trials of SSRI data in children (Jureidini, J.N, 2004). The first of these looked only at Fluoxetine and looked at 315 children ranging in ages from 7 to 18 years of age. It found that the introduction of fluoxetine decreased objective and subjective ratings of depression, diminished the likelihood of recurrence, and demonstrated a lower adverse outcome frequency (suicidal behavior) compared to placebo. While later criticized for seriously inadequate study parameters, the first group also reported that:

1. Paroxetine (Paxil) demonstrated no clinical utility in children and an increased risk for adverse events;

2. Sertraline (Zoloft) produced an outcome superior to placebo in one study, but when unpublished data was reviewed, the clinical significance was no longer found;

3. Citalopram (Celexa) and venlafaxine (Effexor) were not recommended due to poor risk: benefit profiles.

The second independent group compared six studies with 941 children. These subjects were randomly assigned to treatment groups being administered paroxetine, venlafaxine, sertraline, fluoxetine, and placebo. Interesting, the subjective/objective ratings of depression for the treated subjects were found to be statistically insignificant compared to placebo for the parents or significant others (10 different rating scales were used in these 6 studies). However, in contrast, statistical significance was found between placebo and the treatment groups when considering only the physician's reports from the rating scales. Additionally, this review found more adverse events with

paroxetine and sertraline compared to placebo.

Many clinicians will quickly point out the potential inadequacies of these studies. However, in order to ensure the safety of the consumer, the CSM and FDA alike require that pharmaceutical companies generate data that demonstrates their substance's safety for specific use groups and not just that there is an absence of data to suggest that the medications are unsafe. On October 15th, 2004, the FDA published an announcement that they had directed

"manufacturers of all antidepressant drugs to revise the labeling for their products to include a boxed warning and expanded warning statements that alert health care providers to an increased risk of suicidality (suicidal thinking and behavior) in children and adolescents being treated with these agents, and to include additional information about the results of pediatric studies"

However, the FDA did not stop at the SSRIs, but rather produced a "black box warning" for the following medications:

Anafranil (clomipramine HCl)	Paxil (paroxetine HCl)
Aventyl (nortriptyline HCl)	Pexeva (paroxetine mesylate)
Celexa (citalopram HBr)	Prozac (fluoxetine HCl)
Cymbalta (duloxetine HCl)	Remeron (mirtazapine)
Desyrel (trazodone HCl)	Sarafem (fluoxetine HCl)
Effexor (venlafaxine HCl)	Serzone (nefazodone HCl)
Elavil (amitriptyline HCl)	Sinequan (doxepin HCl)
Lexapro (escitalopram oxalate)	Surmontil (trimipramine)
Limbitrol (chlordiazepoxide/amitriptyline)	Symbyax (olanzapine/fluoxetine)
Ludiomil (Maprotiline HCl)	Tofranil (imipramine HCl)
Luvox (fluvoxamine maleate)	Tofranil-PM (impiramine pamoate)
Marplan (isocarboxazid)	Triavil (Perphenaine/Amitriptyline)
Nardil (phenelzine sulfate)	Vivactil (protriptyline HCl)
Norpramin (desipramine HCl)	Wellbutrin (bupropion HCl)
Pamelor (nortriptyline HCl)	Zoloft (sertraline HCl)
Parnate (tranylcypromine sulfate)	Zyban (bupropion HCl)

For psychologists unfamiliar with these, "black box warnings" are designed to highlight special problems, particularly those that are serious, and to give health care professionals a clear understanding of a potential medical complication associated with a drug. Black box warnings provide treating clinicians with important insights as to how a drug may be associated with serious side effects, and ways of prescribing that maximize the drug's benefit: risk ratio.

In its announcement, the FDA reiterated that only fluoxetine had been given approval for the treatment of Major Depressive Disorder in children. It was also restated that that

only sertraline, fluoxetine, fluvoxamine (Luvox), and clomipramine (Anafranil) had been approved for Obsessive/Compulsive Disorder in the same age group.

Providing more evidence for concern, Jick et al (2004) published a study clarifying that the first few weeks of treatment with antidepressants were the most crucial. In reviewing primarily European studies that included 159,810 subjects, all children over 10 years of age, these researchers compared suicidal behavior and other adverse events based upon whether the patient was being administered a single drug (dothiepin) from the older class of TCA (tricyclic antidepressant) versus paroxetine, fluoxetine, or the TCA, amitriptyline. What they discovered was that a successful or completed suicide was nearly 40 times more likely in the first 9 days of treatment. Suicidal behaviors (non-successful) were 4 times more prominent in the first 9 days and 3 times more likely from day 10 through 30. Two things were important to note from the Jick, et al study:

1. Only 68 of 159,810 subjects were reported to have suicidal behaviors, and;

2. Suicidal behaviors and completions did not differ based upon what medications were being administered.

What does this mean for the treating psychologist who cares for a young patient being administered an antidepressant? Currently our role is unclear, however, the FDA directed the following:

"*Pediatric patients being treated with antidepressants for any indication should be closely observed for clinical worsening, as well as agitation, irritability, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. This monitoring should include daily observation by families and caregivers and frequent contact with the physician. It is also recommended that prescriptions for antidepressants be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose*" (underscore by author).

Because psychologists have special knowledge about mental health and psychopharmacology, it is likely incumbent upon us to make certain that the parents and guardians are aware of the current black box warnings, the limitations and strengths of the research regarding the antidepressants pertaining to children, and to assist the parents/guardians/prescribers in the ongoing assessment for adverse effects. While it may be arguable that antidepressant medications represent a very powerful tool in the treatment of depression across the age range, the safety, efficacy, and cost effectiveness of properly provided psychotherapy is well-researched. We should not miss out on the opportunity to remind families, physicians, and 3rd party payers of this critical factor!

References

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About the Author:

Dr. John Courtney is a board certified pediatric neuropsychologist, practicing in South Bend, Indiana. Dr. Courtney also has an M.S. in Clinical Psychopharmcology from Nova Southeastern University and is currently preparing to sit for APA's national psychopharmacology board examination (PEP).