

# SSRIs in children and adolescents

## Where do we stand?

Parents have heard the frightening news reports.  
Here is information to help you answer their questions



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**C**aitlin McIntosh, 12, hanged herself with shoelaces weeks after starting treatment for depression with a selective serotonin reuptake inhibitor (SSRI). Matt Miller, 13, hanged himself in his bedroom closet after taking his seventh SSRI dose. Michael Shivak, 11, slashed his wrists in class—but survived—while taking an SSRI.

These adolescents' parents testified at an FDA hearing Feb. 2 about possible increased risk of suicidality with SSRIs in depressed children and adolescents.

Other families related positive experiences. Sherri Walton said her daughter, Jordan, 14, has achieved "enormous benefit" from taking SSRIs for obsessive-compulsive disorder. Suzanne Vogel-Scibilia told the FDA panel she is convinced that her two children with psychiatric disorders lead full lives because of SSRIs.



Sensitive to the anguish of grieving families but not wanting to deprive seriously depressed children of effective treatment, the FDA is proceeding methodically with its inquiry—probably at least until summer.

In the meantime, this article offers resources to help you answer questions from parents concerned about their children starting or continuing SSRIs. We include pediatric antidepressant dosing recommendations and data on benefits and risks of SSRIs and other reuptake inhibitors in young patients.

**WHY THE FDA INQUIRY?**

SSRI-associated behavioral activation and suicidal ideation in children and adolescents were reported anecdotally, as case reports, in the early 1990s,<sup>1</sup> and more recently.<sup>2</sup> No convincing evidence has shown, however, that SSRIs increase the risk of suicide. In fact, widespread use of SSRIs has been associated with reduced suicide rates.<sup>3</sup>

In May 2003, unpublished data submitted to the FDA from placebo-controlled trials suggested an increased risk of “possibly suicide-related” events and “suicide attempts” in pediatric patients taking paroxetine for major depression. No suicides were reported.

The Medicines and Healthcare Products Regulatory Agency (MHRA)—the United Kingdom’s equivalent of the Food and Drug Administration—responded by warning British physicians against prescribing paroxetine for depressed patients younger than 18. It also ordered a labeling change for paroxetine, contraindicating its use in pediatric major depression.

**The FDA** advised U.S. doctors against using paroxetine for children under age 18 with major depressive disorder and began investigating data on pediatric use of antidepressants, including all approved SSRIs. Since then:

Widespread use of SSRIs has been associated with reduced suicide rates

- In the United States, venlafaxine’s manufacturer changed the drug’s labeling to include increased reports of hostility and suicidality in pediatric trial data. A “Dear Health Care Professional” letter in August 2003 indicated that venlafaxine is not recommended in depressed pediatric patients.

- Britain’s MHRA added pediatric contraindications to labeling of venlafaxine, sertraline, citalopram, and escitalopram in December 2003. The agency opined that fluoxetine is the only SSRI with a favorable risk-benefit profile for pediatric major depression.

- At press time, the FDA had not changed any SSRI labeling.

**At the Feb. 2 public hearing**, the FDA’s Psychopharmacological Drugs Advisory Committee and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee heard public comments from patients, families, and physicians and reviewed the inquiry’s progress. To locate the Web site containing the FDA’s memorandum on this hearing, see *Related resources*.

For the next several months, an expert group at Columbia University is under contract with the FDA to develop a system to classify events that might represent suicidality. The group will then analyze data from 24 studies involving more than 4,000 depressed pediatric patients and nine antidepressants (paroxetine, fluoxetine, sertraline, fluvoxamine, citalopram, bupropion, venlafaxine, nefazodone, and mirtazapine).

**Independent findings.** In January, an American College of Neuropsychopharmacology (ACNP) report concluded that SSRIs do not increase suicidal thoughts or suicide attempts in youth (*Table 1*). An ACNP task force examined the use of SSRIs in more than 2,000 children and adolescents, including all published clinical trial data, unpublished data from several phar-

Table 1

**Suicide deaths, behavior, or ideation  
in clinical trials of youth with major depressive disorder**

Medication	Total youth* in trials	No. of suicide deaths	% of youth with suicidal behavior or ideation**		P value	Statistical significance
			Antidepressant	Placebo		
Citalopram	418	0	8.9%(19)	7.3% (15)	0.5	No
Fluoxetine	458	0	3.6%(9)	3.8% (8)	0.9	No
Paroxetine	669	0	3.7%(14)	2.5% (7)	0.4	No
Sertraline	376	0	2.7%(5)	1.1% (2)	0.3	No
Venlafaxine	334	0	2%(NA)	0%	0.25	No

\* Total number of youth given antidepressants and placebo

\*\* Number inside parenthesis is actual number of youth

NA = Not available

Source: Data from published clinical trials, unpublished clinical trials provided by drug sponsor, and clinical data compiled by the Medicines and Healthcare Products Regulatory Agency of the United Kingdom.

Reprinted with permission of the American College of Neuropsychopharmacology from *Preliminary report of the Task Force on SSRIs and Suicidal Behavior in Youth (executive summary)*, January 2004:18.

maceutical companies, and data reported to Britain’s MHRA. An executive summary is available on the ACNP’s Web site (*see Related resources*).

**DEPRESSION’S IMPACT ON CHILDREN**

The prevalence of depression in youth age 18 and younger is 8.3%,<sup>4</sup> and the rate increases with patient age. Before puberty, common signs of depression include somatic symptoms such as abdominal pain, headaches, and irritability, whereas adolescents are more likely to express feelings of depression and exhibit suicidal behavior. Girls and boys are equally at risk for depression until puberty, when girls begin to outnumber boys and the presentation begins to resemble adult depression.

Untreated pediatric depression is associated with substantial morbidity, including reduced academic performance, substance abuse, interpersonal problems, social withdrawal, and a poor quality of life,<sup>4,5</sup> It also increases the risk of suicide.

**Early-onset depression** is considered a more malignant illness than adult-onset depression because of its effect on development, potential for recurrence,<sup>6</sup> and chronicity into adulthood.<sup>7</sup> The quest to develop appropriate treatment for depressed children and adolescents has been spurred by:

- the substantial risks of morbidity and mortality from childhood depression
- advances in drug treatments for adult-onset depression
- recognition that early-onset depression is treatable.

Physiologically, children are not “mini-adults.” Thus, practicing evidence-based medicine requires separate empirical research for pediatric conditions.

Despite some efforts by the National Institute of Mental Health (NIMH) and the pharmaceutical industry, research in pediatric psychopharmacology and ancillary treatments lags decades behind evidence-based treatment in adults.



**Table 2**

**Efficacy of SSRIs and other newer antidepressants in short-term, placebo-controlled pediatric studies in major depressive disorder**

Drug	Age range	Outcome* (drug vs. placebo)
<b>Paroxetine</b>		
Study 1	12 to 18	Negative†
Study 2	13 to 18	Negative
Study 3	7 to 17	Negative
<b>Fluoxetine</b>		
Study 1	8 to 17	Positive
Study 2	8 to 17	Positive
<b>Sertraline</b>		
Study 1	6 to 17	Trend
Study 2	6 to 17	Negative§
<b>Venlafaxine</b>		
Study 1	7 to 17	Negative
Study 2	7 to 17	Negative
<b>Citalopram</b>		
Study 1	7 to 17	Positive
Study 2	13 to 18	Negative
<b>Nefazodone</b>		
Study 1	12 to 18	Trend
Study 2	7 to 17	Negative
<b>Mirtazapine</b>		
Study 1	7 to 17	Negative
Study 2	7 to 17	Negative

\* Positive ( $P \leq 0.05$ ); Negative ( $P > 0.10$ ); Trend ( $0.05 < P \leq 0.10$ )

† Positive on most secondary endpoints

§ Positive on pooling of 2 studies

Source: Adapted and reprinted from Laughren TP. Memorandum: Background comments for Feb. 2, 2004 meeting of Psychopharmacological Drugs Advisory Committee and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee. Appendix I. Center for Drug Evaluation and Research. Food and Drug Administration, Public Health Service, Department of Health and Human Services.

**FROM TRICYCLICS TO SSRIs**

**Tricyclic antidepressants** (TCAs) were the mainstay in treating childhood depression two decades ago, based on clinical and anecdotal evidence. However, double blind, placebo-controlled studies failed to show that TCAs were effective in treating depressed children and adolescents. The few controlled studies included small samples of children and adolescents, and the methodologies were often flawed.

In the late 1980s, TCA use in children dropped precipitously because of:

- episodes of sudden death in pediatric patients taking desipramine
- introduction of SSRIs as safer alternatives.

The causal link between sudden death and desipramine was tenuous; Biederman's article comparing children exposed versus not exposed to TCAs did not demonstrate a statistically significant difference in sudden death.<sup>8</sup> Even so, fear of cardiotoxicity in children curtailed TCAs' use.

**SSRIs are now** are now usually considered first-line antidepressants for children and adolescents because they are presumed to be safer than TCAs. SSRIs are associated with minimal cardiotoxicity and anticholinergic effects, a wider margin of safety in overdose than TCAs, and demonstrated efficacy.

A 12-week, double-blind study compared paroxetine, 20 to 40 mg/d, imipramine, up to 300 mg/d, and placebo in 275 adolescents with major depression.<sup>9</sup> Patients receiving paroxetine improved significantly more than patients receiving placebo, as measured by reductions in the Hamilton Rating Scale for Depression (HAM-D) total scores and other scales. Response to imipramine was not significantly different from placebo.

Discontinuation rates because of side effects were 9.7% for paroxetine and 31.5% (nearly one-third because of cardiovascular side effects) for imipramine. The average imipramine dosage of 200 mg/d was higher than usual, however.

Table 3

## Recommended antidepressant dosages for children and adolescents

### Selective serotonin reuptake inhibitors

Drug	Dosage	Comments
<b>Citalopram</b>	<b>Once-daily</b> Children: 10 to 20 mg Adolescents: 10 to 40 mg	Antianxiety component Limited pediatric data Less effect on P-450 isoenzyme systems than other SSRIs, with fewer drug-drug interactions claimed
<b>Escitalopram</b>	<b>Once-daily</b> Children: 5 to 10 mg Adolescents: 10 mg	L-isomer of citalopram, purported to have lesser side effects than parent compound No data in children
<b>Fluoxetine</b>	<b>Once-daily</b> Children: 5 to 20 mg Adolescents: 10 to 60 mg	Antianxiety properties More effective than placebo in trials of adolescent depression <sup>11-12</sup> Long half-life; watch for drug-drug interactions
<b>Fluvoxamine</b>	<b>Divided</b> Children: 50 to 100 mg/d Adolescents: 50 to 200 mg/d	Useful in depression with comorbid obsessive-compulsive symptoms No data for pediatric depression
<b>Paroxetine</b>	<b>Once-daily</b> Children: 10 to 20 mg Adolescents: 10 to 40 mg	Similar profile as fluoxetine but shorter half-life Not recommended in pediatric patients (FDA advisory)
<b>Sertraline</b>	<b>Divided</b> Children: 25 to 100 mg/d Adolescents: 50 to 200 mg/d	Less activating and shorter half-life than fluoxetine

### Other reuptake inhibitors

Drug	Dosage	Comment
<b>Bupropion</b>	<b>Divided</b> Children: 75 to 250 mg/d Adolescents: 75 to 400 mg/d	Useful in depression with comorbid attention-deficit/hyperactivity disorder No controlled data in children
<b>Nefazodone</b>	<b>Divided</b> Children: 100 to 300 mg/d Adolescents: 200 to 600 mg/d	5HT <sub>2</sub> -receptor and serotonin-reuptake blocker
<b>Venlafaxine</b>	<b>Divided or once-daily</b> Children: 18.75 to 75 mg/d Adolescents: 37.5 to 150 mg/d	Noradrenergic and serotonergic effects Limited pediatric data; not recommended in depressed pediatric patients (manufacturer advisory)

Source: Adapted and reprinted with permission from Sood B, Sood R. Depression in children and adolescents. In: Levenson JL (ed). *Depression: key diseases series*. Philadelphia: American College of Physicians, 2000:244.



Head-to-head studies of children with obsessive-compulsive disorder have shown fewer side effects with paroxetine compared with clomipramine. Paroxetine's side effects included anxiety and headaches; clomipramine's included headache, tremor, nausea, insomnia, dry mouth and anxiety.<sup>10</sup>

**Efficacy data.** Two double-blind, placebo-controlled studies have shown fluoxetine to be more effective than placebo in treating children and adolescents with depression.<sup>11-13</sup> In general, however, not all SSRIs have shown consistent efficacy in placebo-controlled trials of pediatric major depression. Among 15 such trials submitted to the FDA, three (20%) showed positive results (*Table 2*). The success rate of drug therapy trials for adult major depression is about 50%.

The FDA's Feb. 2 hearing memorandum notes several reasons why the agency does not view these findings as proof that SSRIs lack benefit for pediatric patients. For one, the FDA's program allowing drug companies to apply for pediatric marketing exclusivity—for which the 15 studies were submitted—did not require positive efficacy results.

Clearly, more research is needed to demonstrate the benefits and risks of SSRIs in children and adolescents with major depression and other disorders.

The FDA is investigating a possible increased risk of suicidality with SSRIs in depressed children and adolescents. Until results are known, follow antidepressant labeling that advises caution when prescribing to and monitoring high-risk patients, especially during initial therapy.

**Bottom**Line

## **USING SSRIs SAFELY IN YOUTH**

During its inquiry, the FDA recommended that prescribers observe standard antidepressant labeling language:

- Be cautious when using SSRIs or related antidepressants in major depressive disorder in children and adolescents.
- Supervise high-risk patients, especially during initial drug therapy.

**Monitor suicidality.** When treating depressed youth with SSRIs and other antidepressants, ask about suicide attempts, suicidal thinking, and plans for suicide. As part of informed consent, discuss with parents the potential for suicidal behavior in youth with untreated depression.

Discuss antidepressant side effects, which may include disinhibition and impulsivity. Individualize treatment plans; for example, aggressive and impulsive children require especially careful monitoring for risky or suicidal behavior.

**Rule out bipolar depression** and mixed episodes that are often characterized by marked irritability before prescribing antidepressants to depressed children and adolescents. Early-onset depression is a marker for bipolar disorder in pediatric populations, and bipolar illness may be a possible explanation for behavioral activation and dysphoria when antidepressants are prescribed.

**Minimize side effects.** Children can tolerate moderately high SSRI dosages but are usually started on lower dosages than are used in adolescents and adults (*Table 3*). SSRIs do not show a clear dose-response relationship, but their side effects are considered dose-dependent.<sup>14</sup>

Most-frequent SSRI side effects are nausea, diarrhea, decreased or increased appetite, headaches, restlessness, tremor, and insomnia or hypersomnia. Rare side effects include ecchymoses.<sup>15</sup> Reduced growth, possibly related to growth hormone suppression, has been reported in four boys treated with SSRIs.<sup>16</sup>

**Prevent drug interactions.** SSRIs are rarely used as monotherapy in pediatric patients because of the



## Related resources

- ▶ Food and Drug Administration. Report prepared for public hearing Feb. 2, 2004. [www.fda.gov/ohrms/dockets/ac/04/briefing/4006b1.htm](http://www.fda.gov/ohrms/dockets/ac/04/briefing/4006b1.htm) (click on "Background Memorandum")
- ▶ Preliminary report of the task force on SSRIs and suicidal behavior in youth, Jan. 21, 2004. American College of Neuropsychopharmacology. [www.acnp.org/exec\\_summary.pdf](http://www.acnp.org/exec_summary.pdf)
- ▶ Sood B, Sood R. Depression in children and adolescents. In: Levenson JL (ed). *Depression: key diseases series*. Philadelphia: American College of Physicians, 2000.

### DRUG BRAND NAMES

Bupropion • Wellbutrin  
Citalopram • Celexa  
Escitalopram • Lexapro  
Fluoxetine • Prozac  
Fluvoxamine • Luvox

Nefazodone • Serzone  
Paroxetine • Paxil  
Sertraline • Zoloft  
Venlafaxine • Effexor

### DISCLOSURE

Dr. Sood is a speaker for AstraZeneca, Shire Pharmaceutical Group, and Eli Lilly and Co.

Dr. Elizabeth Weller has received research/grant support from Forest Pharmaceuticals, Organon, and Wyeth Pharmaceuticals and is a consultant to Johnson & Johnson, Novartis, AstraZeneca, and Otsuka Pharmaceutical.

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high rates of comorbidity and severity of mental illness that presents in childhood. Using two or more medications is the rule, not the exception.<sup>17</sup>

SSRIs are highly protein-bound and are metabolized by the cytochrome P-450 isoenzyme system, which increases the likelihood of drug-drug interactions. Thus, be aware of the potential impact of combining SSRIs with other agents.

Some researchers suggest that paroxetine, sertraline, and citalopram's relatively short half-lives (14 to 16 hours) in children may be a rationale for giving the medications twice daily.<sup>18</sup>

**Avoid withdrawal.** The withdrawal syndrome following abrupt cessation of paroxetine, venlafaxine, or fluvoxamine is well known, and its irritability and depression-like symptoms can be quite distressing for patients. Thus, make decisions thoughtfully when discontinuing SSRIs, and plan to taper for 1 to 2 weeks.

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