

## Selective serotonin-reuptake inhibitors and suicidal ideation and behavior in children

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Depression is one of the most common mood disorders among children and adolescents, occurring in approximately 2% of children and 6.5% of adolescents in the United States.<sup>1,2</sup> Between 20% and 40% of these patients may have a relapse within two years. Each episode usually lasts about eight months, and symptoms may include irritability, apathy, hopelessness, decreased concentration, and, in some cases, suicidal thoughts and behaviors. Suicide is one of the leading causes of death in the pediatric population, especially among adolescents.<sup>3</sup> Of children and adolescents who committed suicide, 50–75% suffered from a mood disorder, most frequently depression.<sup>4</sup> Therefore, health care providers must be able to recognize the signs and symptoms of depression in the pediatric population and manage their therapy accordingly.

Psychotherapy and antidepressants have been the primary methods of treating depression in children but are often underused. Less than 50% of adolescent females and under 20% of adolescent males received psychotherapy or antidepressants within the year before their suicide.<sup>5</sup> Thus far, cognitive behavioral therapy (CBT)

and interpersonal therapy have led to significant improvements in adolescents with depression and are considered the preferred psychotherapies in this patient population.<sup>6-9</sup> These therapies may help children and adolescents with mild or moderate depression and serve as adjunct therapy for patients with severe depression.<sup>10</sup> Antidepressants may be most beneficial to those who do not have access to a psychotherapist, lack the time or interest to attend the sessions, or do not respond adequately to psychotherapy alone.

Antidepressants, including tricyclics, selective serotonin-reuptake inhibitors (SSRIs), and atypical agents (e.g., venlafaxine, mirtazapine), have been used to treat depression in children and adolescents. Tricyclics, however, have not been shown to be superior to placebo,<sup>10,11</sup> perhaps because children have an underdeveloped noradrenergic system.<sup>12</sup> Tricy-

clics have more intolerable adverse effects, such as anticholinergic complications, confusion, cardiotoxicity, and drowsiness, than do other antidepressants and are more likely to cause death in the event of an overdose. Safety and efficacy data are lacking for newer agents, such as venlafaxine, which was shown to be ineffective in treating pediatric patients with depression.<sup>13,14</sup> Also, it may increase the risk of suicide-related events. SSRIs have shown greater efficacy in treating depression than placebo and caused more tolerable adverse effects than tricyclics,<sup>9,15-17</sup> making SSRIs the antidepressants of choice. However, there has been an increased concern that SSRIs and other antidepressants may increase the occurrence of suicidal ideation and suicide in children and adolescents.

**Early reports and recent regulatory action.** In 1990, the case reports of six patients who developed suicidal ideation after starting fluoxetine were published.<sup>18</sup> One patient was an adolescent, had recently been hospitalized for depression, and demonstrated psychotic behavior, including paranoia, dissociation, and mild suicidal behavior, before antidepressant therapy. The patient displayed an increased frequency of self-injurious behavior (i.e., head banging, mutila-

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tion) and attempted suicide after fluoxetine was initiated and when the daily dosage was increased from 20 to 80 mg over six weeks.

In June 2003, the United Kingdom's Committee on Safety and Medicines stated that paroxetine and venlafaxine should not be given to children under 18 years of age. Shortly afterward, the Food and Drug Administration (FDA) recommended against treating with paroxetine adolescents and children under age 18 and warned against abrupt discontinuation of the drug.

In March 2004, FDA asked manufacturers of SSRIs and atypical antidepressants to include warning statements in their labeling recommending close observation for the possibility of worsening depression or the emergence of suicidal ideation, self-injurious behavior, and suicide attempts. FDA also urged health care professionals to reevaluate drug therapy should anxiety, mania, agitation, hostility, or akathisia develop in patients.

The data were further analyzed by an FDA advisory committee, which issued a statement in September 2004 that fluoxetine was the only one of the seven products evaluated (fluoxetine, sertraline, paroxetine, citalopram, venlafaxine, nefazodone, and mirtazapine) that showed efficacy in the treatment of depression. However, the committee did acknowledge the increased risk of suicidality associated with antidepressant therapy and recommended that warnings about this increased risk should be placed on all antidepressant labeling. The advisory committee agreed that a patient information sheet should be distributed with every antidepressant prescription. It also voted (15 to 8) to add a black-box warning to all antidepressants' labeling to alert prescribers that children taking these medications are at increased risk for suicidality. It recommended the drugs not be contraindicated in children and adolescents because access

to antidepressants is necessary for those who benefit from them.

**Overview of clinical trials.** Depending on how and which data are analyzed, different authors have arrived at different conclusions regarding SSRI-induced suicidal behavior.<sup>14,19-21</sup> One study involving patients 10–19 years of age demonstrated a decrease in the incidence of suicide after initiation of SSRI therapy.<sup>22</sup> For every 1% increase in SSRI use in adolescents, a decrease of 0.23 suicide per 100,000 adolescents per year was found. On the contrary, a study of approximately 2800 acts of self-injurious behavior demonstrated by adults and adolescents found a higher incidence of self-injurious behavior in patients receiving SSRIs versus other antidepressants.<sup>23</sup> However, these results should be viewed with caution. The presence of confounding factors, such as cultural background, selective prescribing, comorbid psychiatric conditions, drug–drug interactions, and adherence to antidepressant therapy, may reduce the possibility of a causal relationship between SSRIs and suicidal behavior.

SSRIs have shown efficacy in a few randomized controlled studies of children and adolescents.<sup>9,15-17</sup> In one study, patients treated with paroxetine (mean dose, 28 mg daily) demonstrated significantly greater improvements when compared with those who received placebo.<sup>15</sup> Of the 93 patients receiving paroxetine, 5 had suicidal ideations or behaviors, compared with 1 of 87 in the placebo group. Fluoxetine (20 mg daily) has also shown greater efficacy than placebo after two months.<sup>16,17</sup> In one study, 56% of patients showed improvements with fluoxetine versus 33% who received placebo.<sup>16</sup> However, adverse effects were not clearly identified. In another study, fluoxetine demonstrated greater remission rates for depression compared with placebo (41% versus 20%, respectively).<sup>17</sup> Three of 109 patients receiv-

ing fluoxetine discontinued therapy because of agitation, hyperkinesia, and mania, compared with 1 of 101 patients who discontinued placebo because of anxiety.

In another study, 439 patients were randomly assigned to receive fluoxetine alone (10–40 mg daily), CBT alone, fluoxetine (10–40 mg daily) with CBT, or placebo.<sup>9</sup> Results over 12 weeks demonstrated greater efficacy with fluoxetine and CBT (71%) than with monotherapy with fluoxetine (61%), CBT (43%), or placebo (35%). All treatment groups had a decrease in suicidal ideation, and there was no difference between fluoxetine and placebo in the exacerbations of suicidal thoughts. Also, those patients treated with both CBT and fluoxetine had a lower frequency of psychiatric symptoms compared with those who received fluoxetine alone.<sup>9</sup> However, this study did not have a sufficient sample size to determine a statistical difference in suicide attempts between treatment groups.

Whittington and colleagues<sup>14</sup> performed a meta-analysis of published and unpublished data regarding the use of antidepressants in patients 5–18 years old. Five randomized controlled studies were included in their analysis. Paroxetine, sertraline, citalopram, and venlafaxine demonstrated an increased relative risk for suicidal ideation or suicide attempts, ranging between 1.5 and 13.8. Fluoxetine was the only drug that did not cause an increase in the relative risk of suicidal ideation and behavior and demonstrated no increase in suicidal behavior compared with placebo. While it is important to note these results, the studies analyzed were not intended to identify attempted suicide and may not have had the statistical power to determine suicide risk because of their small sample size. Another meta-analysis found that the rate of suicidal acts with fluoxetine did not significantly differ from placebo.<sup>24</sup> Retrospective analysis of 17 double-blind studies, including

over 3000 patients, found that fluoxetine (20–80 mg daily) did not increase patients' risk for suicide. This study mostly evaluated adults; therefore, these conclusions cannot be extrapolated to pediatric patients.

**Mechanisms of SSRI-induced suicidal behavior.** Several hypotheses have attempted to explain the increased risk of suicidal ideation, self-injurious behavior, and suicide attempts caused by SSRIs, including inadequate dosing, activating adverse effects, and nonadherence to drug therapy.

**Inadequate dosing.** Data about the optimal initial and maintenance dosages of antidepressants in children are unclear. *The Pediatric Dosage Handbook*, a widely used reference, generally suggests that children should receive half the initial adult dosage of SSRIs, and the maintenance dosage should be adjusted to achieve efficacy.<sup>25</sup> However, this recommendation may not apply to all children. Pharmacokinetic parameters differ between children and adults. SSRIs are largely metabolized by the cytochrome P-450 (CYP) isoenzymes 2D6 or 3A4, and their clearance may vary among patients. The concentration of these isoforms may be elevated during childhood and approach adult concentrations by puberty. This suggests that greater-than-normal adult doses may be required for children (per kilogram of their body weight) but not for adolescents.<sup>26</sup> It is also unclear if serotonin concentrations and serotonergic-receptor binding rates differ among the pediatric populations. Recent studies suggest that gene variations between serotonin transporters may also play a role in individualizing therapy.<sup>27,28</sup>

Inappropriate initial dosing or adjustment of SSRIs may lead to inadequate response or adverse effects. Plasma concentrations below or above the target level may contribute to self-injurious behavior. Insufficient plasma concentrations of these

agents may be associated with suicidal ideation as a result of undertreated depression. Overdoses may cause adverse effects, such as mania or aggression, which may lead to suicide. Thus, careful adjustment of these agents is warranted. The availability of a liquid formulation may improve adherence, as some caregivers may have difficulty administering tablets or capsules to young children.

**Activating adverse effects.** Currently, fluoxetine is the only SSRI approved by FDA for the treatment of depression in children and adolescents, but other SSRIs are commonly prescribed for this population. Adverse events associated with SSRIs (e.g., sedation, gastrointestinal distress, fatigue, dizziness, and headache) are usually regarded as mild and transient. However, SSRIs have also been associated with hypomania, agitation, insomnia, and akathisia, which some believe may lead to suicidal ideation.<sup>29-31</sup>

Activating adverse effects (e.g., hypomania, agitation, and hyperkinesia) associated with SSRIs may increase suicidal thoughts, self-injurious behavior, and suicide attempts.<sup>20,32</sup> However, this theory has not been proven. Among the SSRIs, fluoxetine is one of the most activating agents.<sup>33</sup> Thus, it would seem that patients receiving fluoxetine should have the highest rate of suicide attempts. However, that idea has been contradicted by two meta-analyses.<sup>14,24</sup> As previously mentioned, other underlying diseases may increase the chance of suicide in patients receiving SSRIs. For example, in patients with undiagnosed comorbid illnesses, such as bipolar disorder, the addition of an SSRI may lead to mania and increase the chance of suicidal thoughts and self-injurious behavior.

**Nonadherence.** Nonadherence with antidepressant therapy may lead to plasma concentrations below the target level or withdrawal syndrome (with abrupt discontinuation), both of which may lead to suicide. A state-

ment from the American Academy of Child and Adolescent Psychiatry reported that 12 of 49 adolescents who committed suicide had been prescribed antidepressants, but none had detectable plasma concentrations of SSRIs at the time of death.<sup>34</sup> Withdrawal effects seen with abrupt discontinuation of antidepressants include mania, nervousness, and agitation. Withdrawal effects may be less of an issue with fluoxetine because of the drug's long elimination half-life (approximately three days), which is about three times higher than the half-lives of other SSRIs. Therefore, adequate concentrations may remain in the body despite nonadherence for a few days.

**Conclusion.** Clinicians must be cautious when initiating antidepressant therapy in children and adolescents. Patients should be monitored closely for any possible adverse effects (including suicidal thoughts and behavior) and adherence to therapy. Antidepressants may increase the risk for suicidal behaviors (i.e., self-injurious behavior, suicide attempts), but clinicians should be cautious in accepting that as a rationale for not using treatment when it is clearly indicated.

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