Sertraline in Children and Adolescents With Obsessive-Compulsive Disorder
A Multicenter Randomized Controlled Trial

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Context.—The serotonin reuptake inhibitors are the treatment of choice for patients with obsessive-compulsive disorder; however, empirical support for this assertion has been weaker for children and adolescents than for adults.

Objective.—To evaluate the safety and efficacy of the selective serotonin reuptake inhibitor sertraline hydrochloride in children and adolescents with obsessive-compulsive disorder.

Design.—Randomized, double-blind, placebo-controlled trial.

Patients.—One hundred eighty-seven patients: 107 children aged 6 to 12 years and 80 adolescents aged 13 to 17 years randomized to receive either sertraline (53 children, 39 adolescents) or placebo (54 children, 41 adolescents).

Setting.—Twelve US academic and community clinics with experience conducting randomized controlled trials.

Intervention.—Sertraline hydrochloride was titrated to a maximum of 200 mg/d during the first 4 weeks of double-blind therapy, after which patients continued to receive this dosage of medication for 8 more weeks. Control patients received placebo.

Main Outcome Measures.—The Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS), the National Institute of Mental Health Global Obsessive Compulsive Scale (NIMH GOCS), and the NIMH Clinical Global Impressions of Severity of Illness (CGI-S) and Improvement (CGI-I) rating scales.

Results.—In intent-to-treat analyses, patients treated with sertraline showed significantly greater improvement than did placebo-treated patients on the CY-BOCS (adjusted mean, −6.8 vs −3.4, respectively; P = .005), the NIMH GOCS (−2.2 vs −1.3, respectively; P = .02), and the CGI-I (2.7 vs 3.3, respectively; P = .002) scales. Significant differences in efficacy between sertraline and placebo emerged at week 3 and persisted for the duration of the study. Based on CGI-I ratings at end point, 42% of patients receiving sertraline and 26% of patients receiving placebo were very much or much improved. Neither age nor sex predicted response to treatment. The incidence of insomnia, nausea, agitation, and tremor were significantly greater in patients receiving sertraline; 12 (13%) of 92 sertraline-treated patients and 3 (3.2%) of 95 placebo-treated patients discontinued prematurely because of adverse medical events (P = .02). No clinically meaningful abnormalities were apparent on vital determinations, laboratory findings, or electrocardiographic measurements.

Conclusion.—Sertraline appears to be a safe and effective short-term treatment for children and adolescents with obsessive-compulsive disorder.

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minimal. Following the placebo lead-in, responses in pediatric OCD appear blind placebo lead-in to eliminate placebo effects. The Experimental Design section describes a randomized, parallel-group trial of sertraline vs placebo in children and adolescents aged 6 to 17 years with OCD. The primary hypothesis was that sertraline would prove to be a well-tolerated and effective treatment for pediatric OCD. We published studies regarding the safety and efficacy of sertraline in pediatric OCD. We know there have been no published studies regarding the safety and efficacy of sertraline in pediatric OCD. We report the results of a 12-week, multicenter, double-blind, placebo-controlled, randomized, parallel-group trial of sertraline vs placebo in children and adolescents aged 6 to 17 years with OCD. The primary hypothesis was that sertraline would prove to be a well-tolerated and effective short-term treatment for pediatric OCD.

METHODS

Experimental Design

The trial began with a 1-week single-blind placebo lead-in to eliminate placebo responses in pediatric OCD. Following the placebo lead-in, patients were randomized within site to 12 weeks of double-blind flexible-dose treatment using a computer-generated randomization algorithm. To ensure that the age distribution was similar for each treatment condition, patients were stratified into 2 age groups: children (aged 6-12 years) and adolescents (aged 13-17 years). Twelve sites representing 6 major geographic regions in the United States participated in the study, which passed human subjects review at each of the participating institutions. All investigators obtained assent of the child or adolescent and written informed consent from parents or legal guardians.

Inclusion and Exclusion Criteria

Patients were male and female outpatients aged 6 to 17 years who met full Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) diagnostic criteria for OCD on clinical interview. At the baseline visit, patients were required to have a score of at least 7 on the National Institute of Mental Health Global Obsessive Compulsive Rating Scale (NIMH GOCs), indicating at least moderate impairment in global functioning from OCD, and a score of 17 or less plus a score of 0 (none) or 1 (minimal) on item 1 (depressed mood) of the 24-item Hamilton Depression Scale, indicating the absence of significant depression. Baseline electrocardiographic and laboratory results were required to be normal or not clinically significant if outside the normal range.

Patients having a primary psychiatric disorder other than OCD on clinical interview were excluded, as were those with medical contraindications to treatment with sertraline or who had participated in a previous sertraline study or been treated with sertraline. Treatment with a neuroleptic, anxiolytic, or antidepressant medication within 2 weeks (or fluoxetine within 5 weeks) prior to the initiation of double-blind treatment or concomitant therapy with any other psychotropic medication was prohibited. Adolescent females of childbearing potential were required to have a negative result for a serum β-human chorionic gonadotropin pregnancy test on day 1 of the placebo lead-in phase. Patients were not permitted to receive behavior therapy or any other form of psychotherapy during the course of the study.

Medication Procedures

Sertraline hydrochloride and pill placebo were packaged in identical blister packs of 25-mg sertraline hydrochloride tablets or identical placebo tablets. The starting dosage for both active treatment and placebo was 25 mg/d for children and 50 mg/d for adolescents. To maximize efficacy, although perhaps at the cost of more adverse effects in those treated with sertraline, dosages were titrated upward in a forced titration procedure by 50 mg/wk to a maximum dosage of 200 mg/d or their maximum tolerated dose during the first 4 weeks of double-blind treatment following a predefined dosing schedule. Further dosage adjustment was permitted only in the event of dose-limiting adverse experiences.

Measures

The primary efficacy measures were the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS), the NIMH GOCs, and the NIMH Clinical Global Impression of Severity of Illness (CGI-S) and Improvement (CGI-I) scales. The CY-BOCS is identical in form and scoring to the widely used adult Yale-Brown Obsessive Compulsive Scale, but the questions are slightly modified for age appropriateness. The CY-BOCS scale ranges from 0 to 40, with a score of 20 indicating moderate severity of obsessive and compulsive symptoms and a score of 10 or below indicating subclinical OCD. The NIMH GOCs has been extensively used in both adult and pediatric OCD trials. It assesses severity of OCD symptoms in relation to their functional impact. Scores of 1 to 3 indicate minimal impairment, scores of 7 or more indicate clinically meaningful OCD symptoms, and scores of 13 to 15 indicate very severe obsessive and compulsive behaviors. The NIMH CGI scales provided clinician- rated overall summary: the CGI-S scale ranges from 1 (normal, not at all ill) to 7 (extremely ill) and the CGI-I scale ranges from 1 (very much improved judgments) to 7 (very much worse judgments).

Efficacy measures were obtained on day 1 of the placebo lead-in phase, 1 week later at the end of the placebo lead-in phase (baseline), and at the end of weeks 1, 2, 4, 6, 8, 10, and 12 of double-blind treatment (or at the time of early termination). Vital signs (eg, blood pressure, pulse) and body weight were recorded at every study visit as were all adverse experiences volunteered by the patient or observed by the investigator. Blood samples for routine hematology and serum chemistry studies and urine samples for routine urinalysis were obtained on day 1 of the placebo lead-in phase and at the end of weeks 1, 2, 4, 6, 8, 10, and 12 of double-blind treatment. A 12-lead electrocardiogram was obtained on day 1 of the placebo lead-in phase and at the end of weeks 1, 4, and 12 of double-blind treatment.

Statistical Analyses

For the efficacy parameters, analysis of covariance models were used, including baseline and any additional postbaseline efficacy data. Except for the CGI-I score, the baseline value was added to the model as a covariate so that the full statistical model included terms for treatment, site, treatment-by-site interaction, age group (6-12 years and 13-17 years), sex, and the interactions of age group and treatment, sex and age group, sex and treatment, and sex, age group, and treatment. Age, weight, Hamilton Depression Scale score, and duration of illness were compared at baseline between the treatment groups using analyses of variance with terms for site and treatment group. Sex, race, and socioeconomic status were compared using...
The average length of treatment for the sertraline group was 74.8 days and for the placebo group it was 75.9 days of 94 possible double-blind treatment days. Seventy-four (80%) of the 92 patients treated with sertraline and 82 (86%) of the 95 individuals treated with placebo completed the 12 weeks of double-blind treatment. Of the 31 patients (18 in the sertraline group and 13 in the placebo group) who discontinued treatment during the double-blind treatment period, only 3 sertraline-treated and 2 placebo-treated individuals discontinued the study because of insufficient clinical response.

As shown in Figure 1, 12 (13%) of 92 patients treated with sertraline and 3 (3.2%) of 95 placebo-treated patients discontinued treatment because of an adverse medical event \( (P = .02) \). Time to discontinuation did not differ between groups. Table 4 summarizes the incidence of adverse events that were statistically associated with sertraline in contrast with placebo treatment. A patient reporting more than 1 episode of the same complaint, even of differing severity, was counted once using the highest level of severity. Among all adverse

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Table 1.—Baseline Comorbidity

<table>
<thead>
<tr>
<th>Comorbid Disorders</th>
<th>Sertraline (n = 92)</th>
<th>Placebo (n = 95)</th>
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<tbody>
<tr>
<td>Any comorbid disorder at baseline</td>
<td></td>
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<tr>
<td>Attention-deficit</td>
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<tr>
<td>hyperactivity disorder</td>
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<tr>
<td>Tic disorder</td>
<td></td>
<td></td>
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<tr>
<td>Anxiety</td>
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<tr>
<td>Depression</td>
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</tbody>
</table>

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**Figure 1** —Study flowchart.
Table 2.—Mean Change From Baseline to End Point in Efficacy Measures: Intent-to-Treat Analysis

<table>
<thead>
<tr>
<th>Efficacy Measure*</th>
<th>Intent-to-Treat</th>
<th>Compler Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted Mean (SEM)</td>
<td>95% Confidence Interval (Sertraline vs Placebo)</td>
</tr>
<tr>
<td>CY-BOCS</td>
<td>-6.8 (0.87)</td>
<td>-3.4 to 1.1</td>
</tr>
<tr>
<td>NIMH Global Obsessive Compulsive Scale</td>
<td>-2.2 (0.29)</td>
<td>-1.3 to 0.1</td>
</tr>
<tr>
<td>NIMH CGI Improvement Scale</td>
<td>2.7 (0.14)</td>
<td>3.3 to 0.1</td>
</tr>
<tr>
<td>NIMH CGI Severity of Illness Scale</td>
<td>-1.0 (0.14)</td>
<td>-0.7 to 0.1</td>
</tr>
</tbody>
</table>

*CY-BOCS indicates the Children's Yale-Brown Obsessive Compulsive Scale; NIMH, National Institute of Mental Health; and CGI, Clinical Global Impressions.

COMMENT

In what is, to our knowledge, the largest placebo-controlled trial of pharmacotherapy for pediatric OCD conducted to date, children and adolescents treated with sertraline fared better than those receiving placebo on 3 of the 4 main dependent measures. Statistically and clinically significant group mean differences emerged at week 3 and persisted for the duration of the study. Eighty percent of sertraline-treated patients and 86% of placebo-treated patients completed treatment. Insomnia, nausea, agitation, and tremor were more common in those receiving sertraline, and more sertraline-treated patients than placebo-treated patients discontinued treatment prematurely because of adverse events. No adverse effects attributable to sertraline use were apparent on vital sign measurement or laboratory or electrocardiographic studies. Thus, we conclude that sertraline appears to be a safe and effective short-term treatment for pediatric OCD.

Because this study used a forced upward titration procedure, no firm statement regarding the relationship between dose and overall efficacy, speed of improvement, or adverse effects can be made. However, experts generally agree that the SSRIs as a group are better tolerated than the nonselective SRI clomipramine. In a study of sertraline in adults with OCD, the most frequently occurring adverse events were nausea, insomnia, somnolence, diarrhea, and decreased libido. A similar adverse effect profile was noted in this study, with the extent of adverse effects in the sertraline group at least in part a function of rapid upward titration to maximum doses. Importantly, the present study failed to reveal significant differences in sertraline's adverse effect profile for children (aged 6-12 years) or adolescents (aged 13-17 years). Thus, the same dosing regimen used in adults appears appropriate for children and adolescents, with dosage tailored to the individual patient as a function of benefits and adverse effects.20

In this regard, a previous fixed-dose study of sertraline in adults with OCD demonstrated that 50-, 100-, and 200-mg dosage conditions were, on average, equal in efficacy.21 Similar conclusions were seen in a fixed-dose study of fluoxetine, also in adults with OCD.22 In both studies, adverse effects appeared to increase with higher doses.23,24 The magnitude of improvement seen in this study is comparable with that seen in other flexible-dose clinical trials of SSRIs for OCD in adults25 and youth.26,27 Hence,
Table 3.—Responder Analysis

<table>
<thead>
<tr>
<th>No. of Responders/ No. of Patients (%)</th>
<th>Relative Rate for Sertraline Hydrochloride Placebo (95% Confidence Interval)</th>
<th>Fisher Exact P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25% Decrease in CY-BOCS score from baseline to end point</td>
<td>49/92 (53) 35/95 (37) 1.45 (1.04-2.00) .03</td>
<td></td>
</tr>
<tr>
<td>NIMH CGI Improvement rating of 1 or 2 (very much or much improved) at end point</td>
<td>39/92 (42) 25/95 (26) 1.61 (1.07-2.43) .02</td>
<td></td>
</tr>
</tbody>
</table>

*CY-BOCS indicates the Children’s Yale-Brown Obsessive Compulsive Scale; NIMH CGI, National Institute of Mental Health Clinical Global Impressions.*

Table 4.—Incidence of Adverse Events

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Sertraline Hydrochloride Placebo P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>37</td>
</tr>
<tr>
<td>Nausea</td>
<td>17</td>
</tr>
<tr>
<td>Agitation</td>
<td>13</td>
</tr>
<tr>
<td>Tremor</td>
<td>7</td>
</tr>
</tbody>
</table>

*Adverse events listed occurred significantly more often in patients treated with sertraline hydrochloride.*

This study was funded by Pfizer Inc, New York, NY.

**References**


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30. Leonard HL, Meyer MC, Swedo SE. Electrocadio


Pott Puffy Tumor Associated With Intranasal Methamphetamine

To the Editor: Pott puffy tumor (PPT) is an anterior extension of a frontal sinus infection that results in frontal bone osteomyelitis and subperiosteal abscess. Since the advent of antibiotics, PPT has been rarely reported and most cases have been described in children and adolescents. We report a case of PPT associated with use of intranasal methamphetamine hydrochloride.

Report of a Case. A 34-year-old woman presented with fever, chills, photophobia, and neck pain for 9 days. Nine months previously, she had developed swelling on her forehead that gradually enlarged over 5 days and then spontaneously drained purulent material. Over several weeks, a fistula developed at the site of the forehead swelling, and was accompanied by intermittent bloody, purulent drainage for approximately 9 months. The patient had no other contributory medical illnesses. However, she had used intranasal and inhaled methamphetamine weekly for 15 years and reported continued intranasal use immediately prior to the development of the forehead lesion. She reported no history of intravenous or other drug use.

Physical examination revealed a sinocutaneous fistula in the midline of the forehead with seropurulent drainage but no local erythema or tenderness. The patient had nuchal rigidity, but findings of the neurologic examination were within normal limits. The remainder of the physical examination was noncontributory. The white blood cell count was 15.3 × 10⁹/L (77 neutrophils and 9 bands). Examination of cerebrospinal fluid, obtained by lumbar puncture, revealed a white blood cell count of 0.5 × 10⁶/L (91% neutrophils, 2% lymphocytes), glucose level of 63 mg/dL (3.5 mmol/L), and a total protein level of 81 mg/dL. A Gram stain showed no organisms and the cerebrospinal fluid cultures and blood cultures were sterile. Computed tomographic scan of the head showed complete opacification of all sinuses with a 1-cm connection between the anterior frontal sinus and the skin. There were no epidural fluid collections or underlying brain parenchymal lesions.

The patient was treated with intravenous clindamycin and ceftriaxone sodium, and oral ciprofloxacin for osteomyelitis with presumed bacterial meningitis secondary to a contiguous focus of infection. On day 5 of her hospital stay, she underwent endoscopic sinus surgery. A second surgical procedure for debridement of the infected frontal bone, ablation of the frontal sinus, and repair of the frontal sinocutaneous fistula was also performed. Aerobic and anaerobic cultures of the purulent drainage from the maxillary sinuses grew Streptococcus milleri and Candida albicans. At the end of 2 weeks, antibiotics were changed to intravenous cefazolin and oral metronidazole and this therapy was continued for 4 additional weeks at home. No further complications occurred at 2 months. The patient was then lost to follow-up.

Comment. Osteomyelitis of the frontal bone is most commonly caused by trauma and frontal sinusitis. We propose that the use of intranasal methamphetamine by this patient contributed to chronic sinus inflammation, which led to the frontal bone osteomyelitis and subperiosteal abscess. Noskin and Kalish have implicated the use of intranasal cocaine as a cause of chronic sinusitis associated with PPT in a 34-year-old man. The sympathomimetic effects of methamphetamine cause vasoconstriction of the mucosal vessels that may result in ischemic injury to the sinus mucosa, and thereby could provide an environment conducive to bacterial growth. We propose that PPT is a potential complication of methamphetamine use.

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CORRECTIONS

Incorrect Value and Wording: In the Caring for the Critically Ill Patient article entitled “Pharmacist Participation on Physician Rounds and Adverse Drug Events in the Intensive Care Unit” published in the July 21, 1999, issue of THE JOURNAL (1999;282:267-270), there was an incorrect value in a table. On page 269, in Table 2, the number of total patients days for Phase 1 in the Study Unit should be 1061 and not 787 as listed. In the “Results” section on the same page, the statement that 300 mg 3 times per day is the correct oral dose of phenytoin is erroneous. It should read “Examples were a recommendation to reduce an excessive dose of intravenous phenytoin from 300 mg 3 times per day to 100 mg 3 times per day. . . .”

Omissions: In the Original Contribution entitled “Sertraline in Children and Adolescents With Obsessive-Compulsive Disorder: A Multicenter Randomized Controlled Trial” published in the November 25, 1998, issue of THE JOURNAL (1998;280:1752-1756), Hans Steiner, MD, of the Department of Psychiatry, Stanford University, Stanford, Calif, was omitted from the list of authors. Additionally, on page 1754, at the end of the second paragraph under the heading “Sample Characteristics,” the following sentences were omitted: “The mean CGI-BOCS score at baseline was 23.4 for patients randomized to sertraline and 22.2 for patients randomized to placebo. The mean NIMH GOCS score at baseline was 9.2 for patients randomized to sertraline and 9.1 for patients randomized to placebo. The mean CGI-5’s score was 4.7 for patients randomized to sertraline and 4.6 for patients randomized to placebo.”