

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 sign 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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APPROXIMATELY 1 in 200 young persons has obsessive-compulsive disorder (OCD),¹ which many believe to be the paradigmatic neuropsychiatric illness.² Individuals with OCD experience obsessions, which are recurrent and persistent thoughts, images, or impulses that are egodystonic, intrusive, and, for the most part, acknowledged as senseless.³

See also p 1784 and Patient Page.

Common obsessions are generally accompanied by distressing negative affects, such as fear, disgust, doubt, or a feeling of incompleteness, and include contamination fears, scrupulosity, fear of harm to self or others, symmetry urges, or hoarding urges. Not surprisingly, persons with OCD typically attempt to ignore, suppress, or neutralize obsessive thoughts and associated feelings by performing compulsions, which are repetitive, purposeful behaviors that are usually performed according to certain rules or in a stereotyped fashion to temporarily neutralize or alleviate obsessions and their accompanying dysphoric affects.⁴ Compulsions can be observable behaviors (eg, hand washing) or covert mental acts (eg, counting). Among children and adolescents with OCD, few receive a correct diagnosis and even fewer receive appropriate treatment.¹

An extensive empirical literature demonstrates that the potent serotonin reuptake inhibitors (SRIs) clomipramine hydrochloride,⁵ fluoxetine,⁶ fluvoxamine,⁷ paroxetine,⁸ and sertraline hydrochloride⁹ are effective treatments for adults with OCD. Although empirical support is more limited, pharmacotherapy for children and adolescents with OCD also relies on SRIs.¹⁰ The earliest pediatric studies were conducted with the tricyclic compound clomipramine.⁵ In the mid 1980s, Flament et al¹¹ reported that clomipramine was statistically superior to

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placebo in a placebo-controlled, double-blind, crossover study. Leonard et al¹² then showed that clomipramine was superior to the predominantly noradrenergic reuptake inhibitor desipramine hydrochloride. Subsequently, an 8-week multicenter, double-blind, parallel comparison of clomipramine vs placebo led to US Food and Drug Administration approval of clomipramine for the treatment of OCD in children and adolescents aged 10 years and older.¹³

Unfortunately, clomipramine causes a wide spectrum of anticholinergic, antihistaminergic, and antiadrenergic adverse effects, including excessive sedation, weight gain, adverse cardiovascular effects, and an increased risk for drug-induced seizures.¹⁴ These difficulties encouraged the search for more effective and better-tolerated treatments for young persons with OCD.¹⁵ One such agent is the selective serotonin reuptake inhibitor (SSRI) sertraline, a naphthylamino compound that specifically blocks neuronal reuptake of serotonin via competitive inhibition at the presynaptic serotonin transporter.¹⁶ Controlled trials of sertraline in adults with OCD demonstrate that sertraline is more effective than placebo¹⁷ at doses ranging from 50 to 200 mg⁹ and that benefits are maintained with continued drug treatment.¹⁸ Controlled studies of fluoxetine and fluvoxamine¹⁹ in pediatric OCD suggest benefits comparable with those seen with clomipramine.¹³ As yet, to our knowledge 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 responders even though placebo responses in pediatric OCD appear minimal.²⁰ 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 all major geographic regions in the United States participated in the study, which passed human subjects review at each of the participating institutions. All investi-

gators 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 criteria²¹ 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),²² 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,²² but the questions are slightly modified for age appropriateness.²³ 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 adult²² and pediatric¹² OCD trials. It assesses severity of OCD symptoms in relation to their functional impact.²⁴ 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).²⁵

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 us-

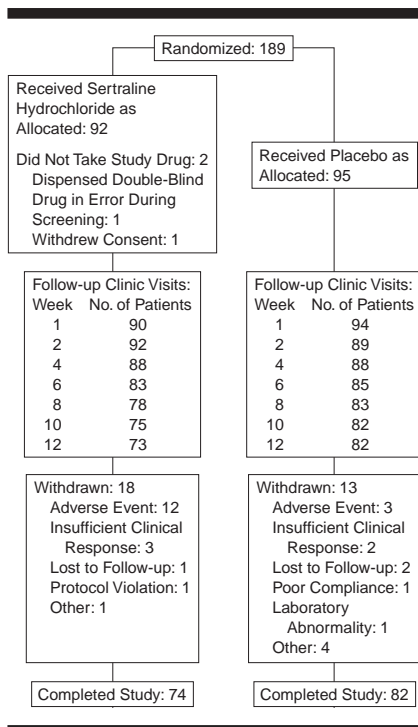


Figure 1.—Study flowchart.

ing χ^2 tests. Changes from baseline in laboratory and vital sign parameters between treatment groups were compared using analysis of variance. The incidence of adverse events was compared between treatment groups using the Fisher exact test. Mean change from baseline to end point in body weight was compared between treatment groups using the Wilcoxon rank sum test. All statistical tests were 2-sided at the .05 α level of significance; assumptions underlying the chosen statistical models were examined prior to conducting the analyses.

RESULTS

Sample Characteristics

Figure 1 shows patient flow through all phases of the study. Two patients randomized to receive sertraline were excluded from the data analyses reported herein. One received active medication and another withdrew consent during the placebo lead-in phase. Full intent-to-treat efficacy analyses including these 2 patients did not appreciably change the results on the main dependent measures. There were no placebo lead-in responders.

One hundred eighty-seven patients entered the double-blind phase of the study and all received at least 1 dose of study medication. Ninety-two patients (53 children and 39 adolescents) were randomized to receive sertraline and 95 (54 children and 41 adolescents) were randomized to receive placebo. The pooled mean age for sertraline and placebo treatment groups was 12.6 years (10.4 years in chil-

Table 1.—Baseline Comorbidity

Most Frequent Comorbid Disorders	No. (%) of Subjects	
	Sertraline Hydrochloride (n = 92)	Placebo (n = 95)
Any comorbid disorder at baseline	19 (21)	17 (18)
Attention-deficit/hyperactivity disorder	6 (7)	3 (3)
Tic disorder	5 (5)	3 (3)
Anxiety	2 (2)	5 (5)
Depression	2 (2)	2 (2)

dren and 15.5 years in adolescents). Among the children, the average duration of OCD was 3.4 years and 4.2 years for the sertraline and placebo groups, respectively. Among the adolescents, the average duration of OCD was 6.1 years and 5.5 years for the sertraline and placebo groups, respectively. Mean baseline scores by treatment group for each of the efficacy measures reveal a patient sample with moderate to severe OCD. The mean CYBOCS 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-S score was 4.7 for patients randomized to sertraline and 4.6 for patients randomized to placebo.

Of those with comorbid conditions, 14 (74%) of 19 in the sertraline group and 14 (82%) of 17 in the placebo group had 1 comorbid diagnosis. Three (16%) of 19 in the sertraline group and 2 (12%) of 17 in the placebo group had 2 comorbid diagnoses; the remainder had 3 or more disorders. As shown in Table 1, the most common comorbid psychiatric diagnosis was attention-deficit/hyperactivity disorder, followed by tic disorders, depression, anxiety disorders, and learning disorders.

Drug Dosing

Reflecting the protocol requirement of forced upward dosage titration to a targeted maximum dosage of 200 mg/d, the mean dosage of sertraline hydrochloride and placebo at end point were 167 mg/d and 180 mg/d, respectively. Among those treated with sertraline hydrochloride, 30 (57%) of 53 children and 32 (82%) of 39 adolescents were receiving a dosage of 200 mg/d at end point. Trough plasma levels of sertraline and its primary active metabolite, desmethylsertraline, normalized for body weight, were not significantly correlated with age or sex and did not predict clinical response in those treated with sertraline.

Efficacy

The effects of sertraline and placebo on the CY-BOCS and NIMH GOCS, CGI-S, and CGI-I ratings at end point are summarized in Table 2. On the most

conservative efficacy analyses, sertraline-treated patients exhibited significantly greater improvement than those taking placebo on the CY-BOCS ($P = .005$) and NIMH GOCS ($P = .02$) and CGI-I scale ($P = .002$). There was a trend favoring sertraline over placebo at end point on the NIMH CGI-S scale that failed to reach the threshold for statistical significance ($P = .09$). Similar but slightly more robust outcomes favoring sertraline were seen in patients who completed all 12 weeks of the study.

Figure 2, Figure 3, and Figure 4 depict the week-by-week scores on the CY-BOCS, NIMH GOCS, and NIMH CGI-I scale for observed cases (available individuals at any point) and at end point (all patients using last observation carried forward). Group mean differences suggestive of greater improvement in the sertraline group than the placebo group are apparent at all study visits subsequent to the end of week 2.

Table 3 presents responder analyses, defined on the CY-BOCS as a greater than 25% decrease in OCD symptoms and on the NIMH CGI scales as much or very much improved. Statistically significant differences favoring sertraline over placebo are apparent on both measures.

Age, race, sex, body weight, baseline OCD score, baseline depression score, comorbidity, socioeconomic status, and plasma sertraline and desmethylsertraline levels did not predict the outcome of treatment.

Safety

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

Table 2.—Mean Change From Baseline to End Point in Efficacy Measures: Intent-to-Treat Analysis

Efficacy Measure*	Intent-to-Treat				Completer Analysis			
	Adjusted Mean (SEM)		95% Confidence Interval (Sertraline vs Placebo)	P Value	Adjusted Mean (SEM)		95% Confidence Interval (Sertraline vs Placebo)	P Value
	Sertraline Hydrochloride	Placebo			Sertraline Hydrochloride	Placebo		
CY-BOCS	-6.8 (0.87)	-3.4 (0.82)	-5.7 to -1.1	.005	-8.0 (0.95)	-4.2 (0.88)	-6.3 to -1.3	.004
NIMH Global Obsessive Compulsive Scale	-2.2 (0.29)	-1.3 (0.27)	-1.7 to -0.1	.02	-2.5 (0.32)	-1.5 (0.30)	-0.1 to -1.9	.03
NIMH CGI Improvement Scale	2.7 (0.14)	3.3 (0.13)	-1.0 to -0.2	.002	2.6 (0.14)	3.2 (0.13)	-1.0 to -0.2	.002
NIMH CGI Severity of Illness Scale	-1.0 (0.14)	-0.7 (0.13)	-0.7 to 0.1	.09	-1.2 (0.16)	-0.8 (0.14)	-0.8 to 0.0	.09

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

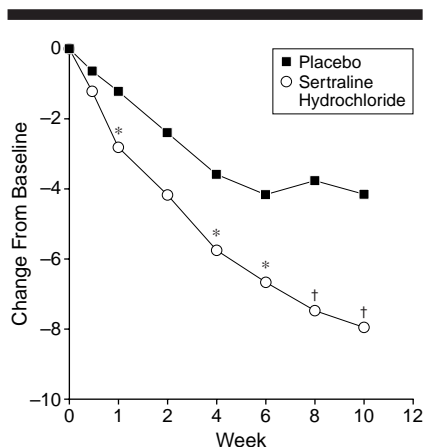


Figure 2.—Weekly Children's Yale-Brown Obsessive Compulsive Scale change scores. Asterisks indicate $P < .05$; daggers, $P < .01$.

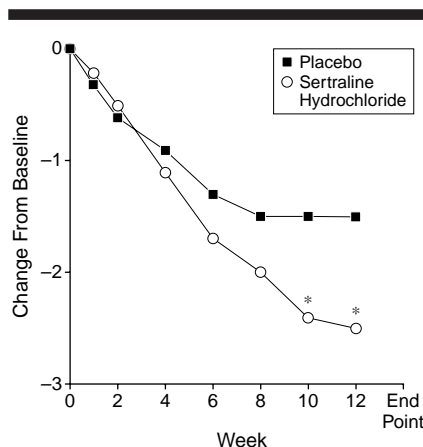


Figure 3.—Weekly National Institute of Mental Health Global Obsessive Compulsive Scale change scores. Asterisks indicate $P < .05$.

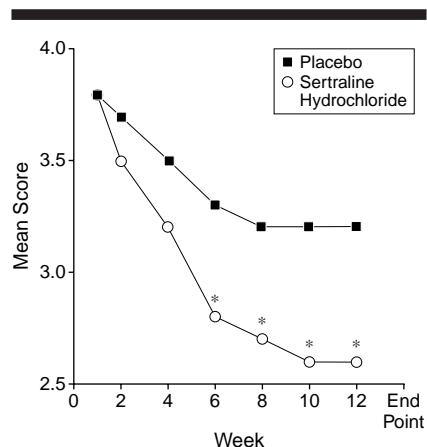


Figure 4.—Weekly National Institute of Mental Health Clinical Global Impressions Improvement Scale change scores. Asterisks indicate $P < .01$.

experiences, there was a statistically significant difference ($P < .05$) in incidence between the sertraline and placebo treatment groups for insomnia, nausea, agitation, and tremor. The majority of adverse experiences fell in the mild-to-moderate range. Importantly, only 2 patients discontinued treatment because of adverse experiences while receiving a dosage of sertraline hydrochloride of less than 100 mg/d.

There were no statistically significant differences in laboratory abnormalities between sertraline-treated patients and placebo-treated patients, and no patients taking sertraline discontinued the study because of laboratory abnormalities. There were no statistically significant differences between the sertraline and placebo groups in blood pressure or pulse, and no clinically significant electrocardiographic abnormalities emerged in either treatment group. A similar percentage of sertraline-treated patients and placebo-treated patients developed electrocardiographic changes, none of which were clinically significant. The mean change in body weight from baseline to final visit of +0.31 kg among the sertraline-treated patients and +1.13 kg among the placebo-treated patients was statistically significant ($P < .05$) but is of minimal clinical importance.

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 bet-

ter tolerated than the nonselective SRI clomipramine.²⁶ In a study of sertraline in adults with OCD, the most frequently occurring adverse events were nausea, insomnia, somnolence, diarrhea, and decreased libido.⁹ 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 dosages. 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 dosage 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.^{10,26}

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.⁹ Similar conclusions were seen in a fixed-dose study of fluoxetine, also in adults with OCD.²⁷ In both studies, adverse effects appeared to increase with higher doses.^{9,27} The magnitude of improvement seen in this study is comparable with that seen in other flexible-dose clinical trials of SRIs for OCD in adults²⁸ and youth.^{13,19,29} Hence,

Table 3.—Responder Analysis*

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

*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*

	Patients, %		P Value
	Sertraline Hydrochloride	Placebo	
Insomnia	37	13	<.001
Nausea	17	7	.05
Agitation	13	2	.005
Tremor	7	0	.01

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

to remain consistent with expert recommendations regarding SRI dosing in OCD,^{10,26} clinicians would be well advised to begin with 50 mg/d of sertraline hydrochloride, moving to maximum dosages by 6 to 8 weeks in nonresponders or partial responders for an adequate acute trial duration of 10 to 12 weeks.

In contrast with tricyclic antidepressants, including clomipramine, which have been reported to cause quinidine-like cardiotoxicity in children and adolescents,³⁰⁻³² the SSRIs show negligible cardiovascular effects.^{15,33} In this context, the absence in this study of significant electrocardiographic changes associated with sertraline is reassuring, and, absent specific indications for doing so, no generic requirement for monitoring cardiovascular or electrocardiographic parameters during sertraline treatment is apparent.

Consistent with findings from other pediatric OCD studies, age, sex, and other measured baseline parameters, including extent of comorbidity, did not predict response to treatment. However, 2 patients who discontinued the study prematurely despite receiving active drug previously were taking medication for attention-deficit/hyperactivity disorder. Although concomitant pharmacotherapy was an exclusion criterion in this study, expert clinical recommendations favor concomitant treatment with a psychostimulant and an SSRI for youth with both attention-deficit/hyperactivity disorder and OCD.^{14,26}

Although treatment with sertraline provided clinically meaningful benefits, as in other studies of SRIs in OCD, the average sertraline-treated patient remained in the mildly ill range on the CY-BOCS at the end of treatment. Accordingly, most

experts agree that the probability of clinical normalization is enhanced by combining pharmacotherapy with OCD-specific cognitive-behavioral psychotherapy.^{26,34} Although current treatments are not generally curative, given a correct diagnosis and skillful treatment most children and adolescents with OCD will improve considerably.

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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 $15.3 \times 10^9/L$ (77 neutrophils and 9 bands). Examination of cerebrospinal fluid, obtained by lumbar puncture, revealed a white blood cell count of $0.5 \times 10^9/L$ (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 ceftazolin 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.¹ 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 Kalish² 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 CY-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 score was 4.7 for patients randomized to sertraline and 4.6 for patients randomized to placebo."