

# Efficacy of Sertraline in the Treatment of Children and Adolescents With Major Depressive Disorder

## Two Randomized Controlled Trials

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**M**AJOR DEPRESSIVE DISORDER (MDD) occurs not only in adults but also in children and adolescents.<sup>1-11</sup> Prevalence rates of up to 3% in children and 8% in adolescents have been reported,<sup>3</sup> and the lifetime prevalence rate for depression in youths aged 15 to 18 years has been estimated at 14% to 15%,<sup>12</sup> which is comparable with that in adults.<sup>13</sup> In general, the clinical course of the disease is similar in pediatric and adult patients, although there is some evidence that early-onset MDD may represent a more pernicious form of the disease.<sup>4,14</sup> Patients diagnosed as having MDD during childhood or adolescence face a 2- to 4-fold greater risk of developing depression as young adults than do children or adolescents without MDD.<sup>14-16</sup>

**For editorial comment see p 1091.**

**Context** The efficacy, safety, and tolerability of selective serotonin reuptake inhibitors (SSRIs) in the treatment of adults with major depressive disorder (MDD) are well established. Comparatively few data are available on the effects of SSRIs in depressed children and adolescents.

**Objective** To evaluate the efficacy and safety of sertraline compared with placebo in treatment of pediatric patients with MDD.

**Design and Setting** Two multicenter randomized, double-blind, placebo-controlled trials were conducted at 53 hospital, general practice, and academic centers in the United States, India, Canada, Costa Rica, and Mexico between December 1999 and May 2001 and were pooled a priori.

**Participants** Three hundred seventy-six children and adolescents aged 6 to 17 years with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*-defined MDD of at least moderate severity.

**Intervention** Patients were randomly assigned to receive a flexible dosage (50-200 mg/d) of sertraline (n=189) or matching placebo tablets (n=187) for 10 weeks.

**Main Outcome Measures** Change from baseline in the Children's Depression Rating Scale-Revised (CDRS-R) Best Description of Child total score and reported adverse events.

**Results** Sertraline-treated patients experienced statistically significantly greater improvement than placebo patients on the CDRS-R total score (mean change at week 10, -30.24 vs -25.83, respectively;  $P=.001$ ; overall mean change, -22.84 vs -20.19, respectively;  $P=.007$ ). Based on a 40% decrease in the adjusted CDRS-R total score at study end point, 69% of sertraline-treated patients compared with 59% of placebo patients were considered responders ( $P=.05$ ). Sertraline treatment was generally well tolerated. Seventeen sertraline-treated patients (9%) and 5 placebo patients (3%) prematurely discontinued the study because of adverse events. Adverse events that occurred in at least 5% of sertraline-treated patients and with an incidence of at least twice that in placebo patients included diarrhea, vomiting, anorexia, and agitation.

**Conclusion** The results of this pooled analysis demonstrate that sertraline is an effective and well-tolerated short-term treatment for children and adolescents with MDD.

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The social and economic costs associated with pediatric MDD are high and may carry over into adulthood, including more frequent hospitalizations and lower educational and earning potential.<sup>14,15,17</sup> In addition, a quarter of adolescents with MDD develop substance

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abuse disorders<sup>3</sup> and approximately half attempt suicide at some time during their lives. Among children with MDD, there is a 4- to 5-fold higher lifetime risk of suicide attempt than in healthy controls.<sup>14,15,18</sup>

Despite the costs and prevalence of the disorder, MDD is frequently underdiagnosed and inadequately treated.<sup>19</sup> For pediatric patients, this problem has been compounded by the discouraging results of early psychopharmacological studies, in which tricyclic antidepressants were consistently found to be no more effective than placebo in treating depressed youths.<sup>20</sup> On the basis of their good safety profile and established efficacy in treatment of adults with MDD, selective serotonin reuptake inhibitors (SSRIs) are routinely cited as the best available treatment option for depressed children and adolescents.<sup>21,22</sup> Empirical evidence of the effectiveness of SSRIs in this patient population has been limited, however. Several small uncontrolled trials of SSRIs<sup>23-28</sup> and a single-center (N=96) placebo-controlled trial of fluoxetine<sup>29</sup> have suggested efficacy. Published reports of 2 large multicenter, placebo-controlled studies of fluoxetine<sup>30</sup> and paroxetine<sup>31</sup> also reported favorable results, but statistical significance was not achieved for their primary end points.

Encouraging results have been reported in 3 small, open-label studies of sertraline in adolescents with MDD<sup>32-34</sup> and in a retrospective chart review of pediatric patients.<sup>35</sup> Herein, we report the pooled results of 2 identically designed, concurrently conducted 10-week international, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials of sertraline vs placebo in children and adolescents with MDD.

## METHODS

### Study Participants

Participants were outpatients aged 6 to 17 years who met the diagnostic criteria for MDD, as defined in the *Diagnostic and Statistical Manual of Mental Dis-*

*orders, Fourth Edition (DSM-IV)*<sup>1</sup> and as determined by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL).<sup>36</sup> For study entry eligibility, these diagnostic criteria had to be met at the first and third visits during a 2-week screening period and the current episode of major depression had to be of at least 6 weeks' duration. At all 3 visits during the screening period, patients were required to have a Children's Depression Rating Scale—Revised (CDRS-R) score of at least 45<sup>37,38</sup> and a Clinical Global Impression of Severity of Illness (CGI-S) rating of at least 4,<sup>39</sup> indicating at least moderate severity of illness. Exclusion criteria included current, primary, DSM-IV–defined diagnosis of attention-deficit/hyperactivity disorder, conduct disorder, obsessive-compulsive disorder, or panic disorder; history of bipolar disorder; any current psychotic features; and history of psychotic disorders or autistic spectrum disorders. Patients who had previously attempted suicide or who were judged to pose a significant suicidal or homicidal risk were also excluded. Patients were also excluded if screening electrocardiographic or laboratory test results, vital signs, or body weight were clinically significantly outside the normal range. Other exclusion criteria included a positive serum  $\beta$ -human chorionic gonadotropin pregnancy test (among girls aged 12-17 years) at the second screening visit, previous enrollment in a sertraline study, medical contraindications to treatment with SSRIs, and history of failure to respond to a clinically adequate dosing regimen of an SSRI. Patients were required to be free of psychotropic medication (with the exception of diphenhydramine or chloral hydrate as sleep aids) for at least 2 weeks (at least 4 weeks for fluoxetine) prior to initiation of double-blind study drug treatment.

### Study Design

The 2 trials, developed in response to a US Food and Drug Administration

(FDA) written request, were identically designed and were conducted at 53 hospital, general practice, and academic centers in the United States, India, Canada, Costa Rica, and Mexico. Participation in the study was based on inspection of the study site by 1 of the authors (C.W.) or a designate. Criteria for investigator participation included but was not limited to previous experience with multicenter research trials, expertise in pediatric psychiatry, and a clear understanding of Good Clinical Practices, as outlined in the US Code of Federal Regulations. Additionally, study conduct was reviewed at investigators' meetings, and all investigators who conducted interviews using the CDRS-R were required to first pass a certification test. During the study, all sites were regularly monitored. When necessary, additional training regarding completion of study documents, retention of source documents, and conduct of ratings was provided on a personal level. All data collected were reviewed for errors in formatting and for inconsistency.

Enrollment began in December 1999 and follow-up ended in May 2001. Both trials were approved by institutional review boards or ethics committees for each study center. Informed assent or written permission of the child or adolescent and written informed consent of at least 1 parent or legal guardian were obtained.

The trials began with the 2-week pretreatment screening period. During these screening visits, diagnosis of MDD was confirmed using the K-SADS-PL and clinical history and symptom severity was assessed using the CDRS-R and CGI-S. Physical and laboratory evaluations were performed at the second screening visit. At the third screening visit (baseline), patients who remained eligible for study entry were randomly assigned to double-blind receipt of either sertraline or matching placebo for 10 weeks in a 1:1 ratio using a computer-generated randomization code. To ensure that each treatment group included similar numbers

of younger and older children, patients were stratified into 2 age groups: children (aged 6-11 years) and adolescents (aged 12-17 years). Study drug was packaged in identical blister packs containing 25-mg and/or 50-mg sertraline tablets or matching placebo. For all patients, treatment was initiated at a dosage of 25 mg/d for the first 3 days and was continued at a dosage of 50 mg/d through the end of the second week. Thereafter, in the absence of dose-limiting adverse events, the dosage could be flexibly titrated upward in increments of 50 mg/d every 2 weeks to a maximum of 200 mg/d until a satisfactory clinical response was achieved. Both patients and clinicians were blinded to group assignment.

With the exception of diphenhydramine and chloral hydrate, which could be used intermittently as sleep aids, concomitant treatment with a psychotropic drug was not permitted. Patients were not permitted to receive cognitive behavioral therapy during the study. Other types of psychotherapy were permitted, provided that they did not specifically address issues of depression and had been under way for at least 2 months prior to the initial screening visit. Patients could be discontinued from the study at an investigator's discretion for reasons such as adverse events and failure to improve despite increases in the study drug dosage.

### Outcome Measures, Schedule of Assessments, and Sample Size

The primary efficacy rating scale was the CDRS-R, a validated 17-item, clinician-rated instrument that measures the severity of a patient's depressive symptoms, with total possible scores ranging from 17 to 113. Fourteen of the 17 items are rated on a scale from 1 to 7, with an item score of 3 suggestive of mild, 4 or 5 moderate, and 6 or 7 severe symptoms. The other 3 items are rated on a scale from 1 to 5. Both children and their parents provide input into the first 14 items of the scale. A child's nonverbal behavior is rated by the observer for items 15 through 17. The prospectively de-

finied primary efficacy outcome measure was the CDRS-R Best Description of the Child total score, which is based on the highest (most severe) rating provided for each item by a valid, reliable source, in the judgment of the investigator; sources included the child, parent or legal guardian, and other available sources.<sup>37,38</sup> Secondary efficacy measures included the proportion of CDRS-R responders, defined a priori as patients who had at least a 40% decrease in the adjusted CDRS-R total score (CDRS-R total minus 17, the minimum possible total score); scores on the CGI-S and the Clinical Global Impression of Improvement (CGI-I) scales, clinician-rated instruments that assess a patient's severity of illness and global improvement, respectively<sup>39</sup>; and the proportion of CGI-I responders, defined as patients with a CGI-I score of 2 or lower ("very much" or "much" improved). The CDRS-R and CGI-S measurements were collected at all 3 screening visits and, along with the CGI-I, at the end of weeks 1, 2, 3, 4, 6, 8, and 10 of double-blind treatment (or at the time of early discontinuation).

Patient-rated secondary efficacy measures included the Multidimensional Anxiety Scale for Children (MASC), which is used to assess symptoms of anxiety<sup>40</sup>; the Children's Global Assessment Scale (CGAS), which measures a patient's social functioning<sup>41</sup>; and the total score on the 15-item Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q), a measure of a patient's quality of life (Jean Endicott, PhD, unpublished data, 2002). This scale was adapted from the Q-LES-Q, a validated instrument that assesses quality of life in adults and that has been shown to be sensitive to drug-placebo differences in mood and anxiety.<sup>42</sup> These assessments were made at baseline and at the end of week 10 of double-blind treatment (or at the time of early discontinuation).

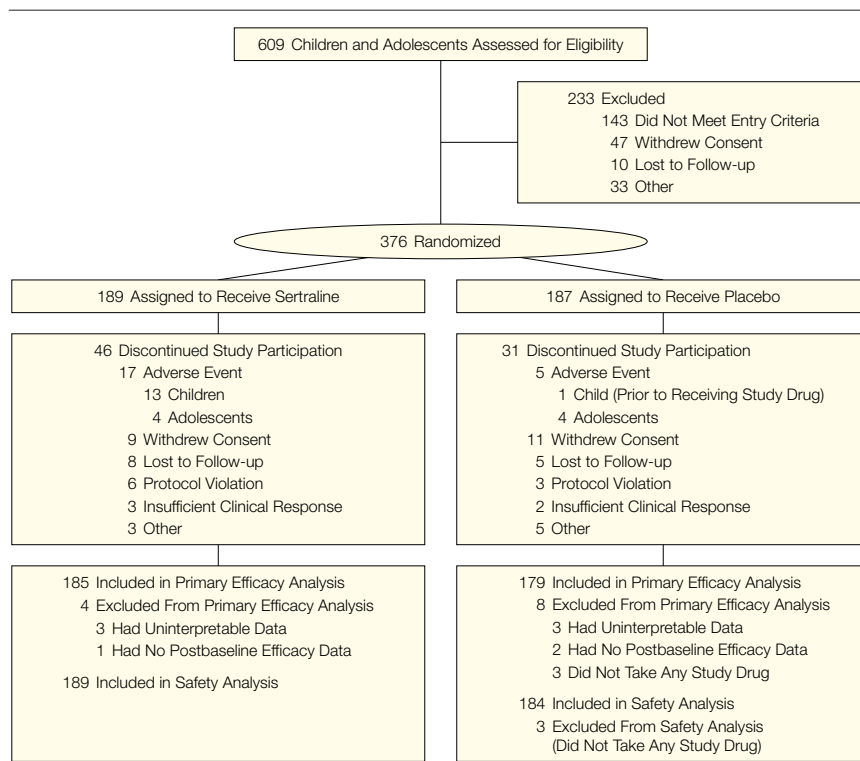
Safety data were collected from the first day of double-blind study drug receipt through 7 days after the last dose of double-blind study drug was taken and included vital signs (blood pres-

sure and pulse), body weight, and all adverse events reported by patients or observed by investigators. A serious adverse event was defined, according to established criteria, as any event that resulted in death or was life-threatening or that resulted in inpatient hospitalization or prolongation of a hospital stay, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Blood samples for routine hematologic and serum chemistry studies and urine samples for routine urinalysis and drug testing were obtained at screening and the end of weeks 4 and 10 (or at the time of early discontinuation). Thyroid function was tested at screening and the pregnancy test was repeated at the end of weeks 4 and 10. A 12-lead electrocardiogram was obtained and a physical examination was performed at screening and the end of week 10 (or at the time of early discontinuation).

Based on the single-center study reported by Emslie et al,<sup>29</sup> a sample size for each trial of 160 patients, with 80 patients per treatment group, was calculated to provide 88% power for a 2-sided test at an  $\alpha$  level of .05 to detect differences between treatment groups. The studies were not powered to detect differences between treatment groups within age groups.

### Statistical Analyses

Data from both studies were pooled in a prospectively defined combined analysis. Using a repeated-measures mixed-model analysis, the mean changes from baseline to each postbaseline visit in the CDRS-R total and the CGI-S score were compared between treatment groups. For each measure, the mean changes from baseline to each postbaseline visit week were then averaged to give a mean overall change from baseline, and the mean overall changes from baseline were compared between treatment groups. The model included the baseline effect as covariate, the random subject effect, and the fixed effects of site, treatment, age group, week, and week-by-treatment interaction. The same mixed model (without the baseline

**Figure 1.** Flow of Patients Through the 2 Trials

effect) was used to compare the CGI-I scores at each postbaseline visit as well as the mean overall CGI-I score in each treatment group. Categorical variables (proportions of CDRS-R responders and CGI-I responders at study end point) were compared between treatment groups using Cochran-Mantel-Haenszel methods with centers as strata. Changes from baseline to study end point in the MASC, CGAS, and PQLS-Q total scores (using the last-observation-carried-forward method) were compared between treatment groups using an analysis of covariance model that contained study treatment group, age group, and baseline effects. As described in the statistical analysis plan, centers with fewer than 4 patients were combined to form 1 pooled center within each trial, and an additional pooled center was generated from centers with exactly 4 patients. This “sort and pool” procedure was chosen as the most objective and conservative way to pool because selective factors such as location and language/culture

were not used. For all statistical tests, a 2-sided  $P \leq .05$  was considered significant. Assumptions regarding the linearity of data were made in the analysis plan and were tested following database release. No gross violation of linear model assumptions was detected; therefore, nonparametric analyses were not performed. Descriptive statistics were used to summarize safety results. SAS version 8.2 (SAS Institute Inc, Cary, NC) was used for the efficacy analysis and SAS version 6.12 was used for safety data.

## RESULTS

### Patient Disposition

As shown in FIGURE 1, 376 patients were randomly assigned to double-blind treatment with either sertraline ( $n = 189$ ) or placebo ( $n = 187$ ). All 189 patients randomized to sertraline and 184 of the patients randomized to placebo received at least 1 dose of double-blind study drug and were included in the safety evaluation. Patients were randomized by the following countries: United

States, 297; India, 44; Costa Rica, 16; Canada, 14; and Mexico, 5. The intention-to-treat population was modified as follows: 1 sertraline-treated and 2 placebo patients were excluded from the efficacy analysis because no postrandomization efficacy data were collected, and 3 sertraline-treated and 3 placebo patients, all from 1 US site, were excluded because of problems with data collection. Thus, 185 sertraline-treated patients (98%) and 179 placebo patients (97%) were included in the efficacy analysis. Forty-six sertraline-treated patients (24%) and 31 placebo patients (17%) discontinued the study early. Among patients treated with sertraline, the most common reasons for discontinuation were adverse events ( $n = 17$ ; 9%), withdrawal of consent ( $n = 9$ ; 5%), and loss to follow-up ( $n = 8$ ; 4%). Similar proportions of placebo patients discontinued from the study because they withdrew consent ( $n = 11$ ; 6%) or were lost to follow-up ( $n = 5$ ; 3%); fewer placebo patients ( $n = 5$ , 1 of whom had not received study drug; 3%) discontinued because of adverse events. This difference was more apparent in children, among whom 13 sertraline-treated patients but no placebo patients discontinued because of adverse events.

### Demographic and Background Characteristics

The 2 treatment groups were evenly balanced with respect to race, weight, clinical characteristics, and psychosocial stressors at baseline (TABLE 1). There was a statistically significant between-group difference in sex (57% of sertraline-treated and 45% of placebo patients were female;  $P = .02$ ) but no significant interaction by age group for the primary and secondary efficacy variables. The majority of patients in both treatment groups ( $\geq 86\%$ ) were in their first lifetime MDD episode, whereas the others ( $< 14\%$ ) were having a recurrent episode. In both subsets of patients, onset of illness occurred at approximately 10 years of age. There were no statistically significant differences in mean baseline CDRS-R or CGI-S scores between

treatment groups. Nearly 40% of patients had at least 1 comorbid psychiatric disorder, with the most common (occurring in  $\geq 5\%$  of patients) being oppositional defiant disorder, anxiety, adjustment reaction, and phobic disorders. More than half of patients had a family history of MDD. The most common stressors included parental divorce or separation and death of a relative or friend. Only about half of patients were living with their biological father.

### Efficacy

As can be seen in FIGURE 2 and TABLE 2, sertraline-treated patients exhibited significantly greater improvement over the course of the study than those receiving placebo on the CDRS-R (mean change in scores of  $-22.84$  vs  $-20.19$ , respectively;  $P = .007$ ), as well as on the CGI-S and CGI-I. Similar outcomes favoring sertraline were observed among patients who completed all 10 weeks of double-blind treatment (mean changes in the CDRS-R total score of  $-30.24$  vs  $-25.83$ , respectively,  $P = .001$ ; and in the CGI-S of  $-1.99$  vs  $-1.58$ , respectively,  $P = .001$ ; and mean CGI-I scores of 2.02 and 2.30, respectively,  $P = .009$ ). Week-by-week analyses showed that significant differences in favor of sertraline were apparent as early as week 1 on the CGI-I and week 3 on the CDRS-R and the CGI-S ( $P < .05$ ).

The adjusted mean change from baseline to study end was assessed for the individual items of the CDRS-R. Statistically significantly greater improvement was noted with sertraline treatment for 5 of the 17 items, including irritability ( $P < .001$ ), low self-esteem ( $P = .02$ ), excessive weeping ( $P = .003$ ), listless speech ( $P = .005$ ), and hypoactivity ( $P = .03$ ). The change in depressed feelings was of borderline significance ( $P = .05$ ), as was difficulty having fun ( $P = .09$ ). No statistically significant difference was noted between treatment groups for suicidal ideation ( $P = .78$ ), and the mean change was of similar magnitude between sertraline ( $-0.58$ ) and placebo ( $-0.60$ ).

Although the study was not powered to detect differences between age

**Table 1.** Baseline Demographic, Clinical, and Psychosocial Characteristics of Patients by Treatment Group\*

Characteristics	Sertraline (n = 189)	Placebo (n = 187)
Demographic characteristics		
Sex		
Male	81 (42.9)	103 (55.1)
Female	108 (57.1)	84 (44.9)
Age group, y		
6-11 (Children)	86 (45.5)	91 (48.7)
12-17 (Adolescents)	103 (54.5)	96 (51.3)
Race		
White	135 (71.4)	130 (69.5)
Asian	26 (13.8)	23 (12.3)
Hispanic	15 (7.9)	19 (10.2)
Black	7 (3.7)	9 (4.8)
Other	6 (3.2)	6 (3.2)
Clinical characteristics		
Patients with single-episode MDD, mean (range)†		
Age at onset of illness, y	10.0 (1.3-16.8)	10.1 (1.2-16.9)
Duration of illness, mo	22.1 (1.5-107.6)	19.1 (1.1-119.3)
Patients with recurrent MDD, mean (range)†		
Age at onset of illness, y	9.6 (3.0-15.8)	10.3 (4.0-14.5)
Duration of illness, mo	43.7 (3.0-132.0)	39.8 (6.0-108.0)
CDRS-R score, mean (SD)‡	64.3 (11.0)	64.6 (11.0)
CGI-S score, mean (SD)§	4.6 (0.6)	4.5 (0.7)
Psychosocial characteristics		
$\geq 1$ Other psychiatric disorder	73 (38.6)	71 (38.0)
Family history of MDD	97 (51.3)	104 (55.6)
Parents were divorced or separated	80 (42.3)	86 (45.9)
Experienced death of close family member/friend	73 (38.6)	64 (34.2)
Biological mother living in same household	164 (86.7)	168 (89.8)
Biological father living in same household	92 (48.6)	98 (52.4)

Abbreviations: CDRS-R, Children's Depression Rating Scale-Revised Best Description of Child total score; CGI-S, Clinical Global Impression of Severity of Illness scale; MDD, major depressive disorder.

\*Data are expressed as No. (%) unless otherwise indicated.

†For sertraline, n = 171 with single episodes and n = 18 with recurrent episodes; for placebo, n = 161 with single episodes and n = 26 with recurrent episodes.

‡For sertraline, n = 185 and for placebo, n = 179 patients in efficacy analysis.

§For sertraline, n = 185 and for placebo, n = 178 patients in efficacy analysis.

groups, a slightly greater difference in the CDRS-R mean change between treatment groups was noted in adolescents (sertraline,  $-21.55$  vs placebo,  $-18.20$ ;  $P = .01$ ) than in children (sertraline,  $-24.05$  vs placebo,  $-22.20$ ;  $P = .19$ ). Following 10 weeks of treatment, the difference in CDRS-R scores was of borderline significance in children (sertraline,  $-31.44$  vs placebo,  $-27.56$ ;  $P = .05$ ) and remained significant in adolescents (sertraline,  $-28.95$  vs placebo,  $-24.11$ ;  $P = .01$ ).

At study end point, using the last observations carried forward and the Cochran-Mantel-Haenszel method of analysis between treatment groups, 69% of sertraline-treated patients and 59% of placebo patients met the CDRS-R

responder criteria ( $P = .05$ ), and 63% of sertraline-treated patients compared with 53% of placebo patients met the CGI-I responder criteria ( $P = .05$ ). In addition, significantly more sertraline-treated patients than placebo patients met the CDRS-R responder criteria at the end of weeks 1, 3, and 10 and the CGI-I responder criteria at the end of weeks 1, 2, 3, 4, and 10 ( $P < .05$ ). With a 10% difference in responder rates for both the CDRS-R and CGI-I, the number needed to treat to expect a difference in response between sertraline and placebo would be 10 using either criterion. Patients treated with sertraline also had numerically better scores at study end point compared with placebo patients on the MASC,

PQ-LES-Q, and CGAS (Table 2). However, the differences between treatment groups did not reach statistical significance.

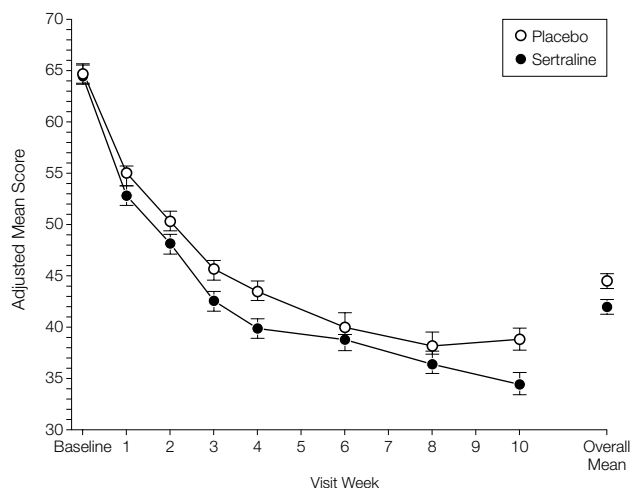
**Tolerability**

The mean dosage of study drug administered to patients who completed 10 weeks of double-blind treatment was 131 mg/d of sertraline and 144 mg/d of placebo equivalent, and the median duration of exposure to study drug was the same in both treatment groups (68 days). Sertraline in the dosage range of

50 to 200 mg/d was generally well tolerated. In the majority (>90%) of patients, adverse events were mild or moderate in intensity. There were 4 adverse events that occurred in at least 5% of sertraline-treated patients and with an incidence of at least twice that in placebo patients: diarrhea, vomiting, anorexia, and agitation (TABLE 3). Seventeen sertraline-treated patients (9%) discontinued the study because of adverse events; 13 of these patients were children. Seven sertraline-treated patients and 6 placebo patients had

adverse events that met the established criteria for a “serious” adverse event, including suicide attempt (2 sertraline and 2 placebo), suicidal ideation (3 sertraline), and aggressive reaction (1 sertraline), as well as medical hospitalizations (1 sertraline and 4 placebo). There were no clinically important differences between the 2 treatment groups with respect to laboratory test, vital sign, physical examination, or electrocardiographic findings. The mean change in body weight from baseline to the final visit was -0.38 kg among patients treated with sertraline and +0.78 kg among placebo patients ( $P=.001$ ).

**Figure 2.** Weekly and Overall Adjusted Mean CDRS-R Scores



CDRS-R indicates Children’s Depression Rating Scale–Revised Best Description of Child total score. Data are least square means at each visit week, with mean scores averaged to give the overall mean, from a repeated-measures mixed-model analysis with age category, site, treatment, week, and week-by-treatment interaction used as fixed effects, subject as a random effect, and baseline effect as a covariate. Error bars indicate SE of the adjusted means, derived from the repeated-measures mixed-model procedure. *P* values are as follows: week 1,  $P=.09$ ; week 2,  $P=.08$ ; week 3,  $P=.01$ ; week 4,  $P=.008$ ; week 6,  $P=.37$ ; week 8,  $P=.18$ ; week 10,  $P=.001$ ; and mean response,  $P=.007$ .

**COMMENT**

In the trials reported here, sertraline was found to be more effective than placebo for treatment of pediatric MDD, with statistically greater improvement occurring as early as week 3. Of the 3 randomized, double-blind, placebo-controlled trials of an SSRI in pediatric MDD that have been published to date,<sup>29-31</sup> only 1, the study by Emslie et al<sup>29</sup> of fluoxetine, reported statistically significantly better results for the prospectively defined primary end point, and this was a comparatively small ( $n=96$ ) single-center trial. Thus, our trials describe the largest positive psychopharmacological study of pediatric MDD, using an international multicenter study design.

The significance of the results is clinically as well as statistically relevant.

**Table 2.** Secondary End Point Measures

Measures	Baseline Score, Mean (SD)		Adjusted Overall Score, Mean (SE)*		Adjusted Change in Score From Baseline, Mean (SE)*		<i>P</i> Value†
	Sertraline	Placebo	Sertraline	Placebo	Sertraline	Placebo	
CGI-I	NA	NA	2.56 (0.06)	2.75 (0.06)	NA	NA	.009
CGI-S	4.57 (0.64)	4.54 (0.66)	3.33 (0.05)	3.55 (0.05)	-1.22 (0.05)	-1.01 (0.05)	.005
CGAS	50.21 (7.07)	49.71 (7.17)	66.00 (1.04)	64.69 (1.04)	16.04 (1.04)	14.74 (1.04)	.38
MASC	51.06 (19.0)	51.85 (20.09)	45.90 (1.17)	48.35 (1.16)	-5.56 (1.17)	-3.11 (1.16)	.14
PQ-LES-Q	49.43 (10.82)	48.92 (10.94)	55.63 (0.68)	53.85 (0.68)	6.46 (0.68)	4.68 (0.68)	.07

Abbreviations: CGAS, Children’s Global Assessment Scale; CGI-I, Clinical Global Impression of Improvement scale; CGI-S, Clinical Global Impression of Severity of Illness scale; MASC, Multidimensional Anxiety Scale for Children; NA, not applicable; PQ-LES-Q, Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire.

\*For the CGI-I and CGI-S, least square means and SEs are provided from a repeated-measures, mixed-model analysis with age category, site, treatment, week, and week-by-treatment interaction used as fixed effects in the model and subject used as a random effect. Baseline CGI-S score was used as a covariate for the analysis of CGI-S. Change from baseline of CGI-S and observed value of CGI-I were analyzed. For the CGAS, MASC, and PQ-LES-Q, last-observation-carried-forward least square means and SEs are provided from analysis of covariance, including protocol number, treatment, age, and baseline effects. Repeated-measures analysis was not used for these end points because values were collected only at baseline and study end.

†*P* values were derived from *t* tests and are the same for both adjusted overall scores and adjusted changes in scores.

Variability of response is typical in pediatric trials and was clearly evident in our study, as demonstrated by the high placebo response rates.<sup>43</sup> Larger variation in response is expected with greater numbers of participating sites because random errors from subject and measurement variation (particularly with subjective measurements) increase with a larger number of investigators with different degrees of experience.<sup>44,45</sup> We used a large number of sites (53) compared with a relatively small number of sites in the fluoxetine studies (15 and 1).<sup>29,30</sup> Additionally, the multinational nature of this study possibly contributed to the variability seen. While no statistically significant treatment-by-center, study, sex, or age interactions were noted, this does not entirely preclude an effect of variability, as long as the effect size from center to center was similar. The fact that no placebo-controlled study of tricyclic antidepressants in children has ever shown significant difference from placebo<sup>20</sup> suggests that even though the differences observed in this study were numerically small, they are nonetheless important.

Mean baseline levels of symptom severity were moderate to severe, as judged by the CDRS-R total scores, and these levels were mild following 10 weeks of treatment. Additionally, the degree of drug-placebo difference was similar to that observed with fluoxetine,<sup>30</sup> which was recently approved by the FDA for treatment of pediatric MDD. In fact, the magnitude of response was greater for sertraline (the mean change from baseline to study end point in CDRS-R total score was -22.0 for fluoxetine vs -14.9 for placebo; mean change from baseline to study end point in CDRS-R total score was -27.31 for sertraline vs -23.89 for placebo). A larger-than-expected percentage of patients in the fluoxetine study had self-rated depression scores that were in the lower range of severity, and approximately one third of those patients had comorbid attention-deficit/hyperactivity disorder, while less than 10% (36/376) of our patients did. It is unknown, however, whether these dif-

ferences account for the differential treatment responses observed between the fluoxetine study results and ours.

The treatment effect size observed in these studies was modest in comparison with that typically observed in adult studies.<sup>46</sup> In part, this appears to be related to the relatively high rate of response to placebo in our patient sample (53%, CGI-I response rate). High placebo response rates have been a consistent feature of psychopharmacological studies of depressed adults,<sup>46</sup> and although studies of depressed youths are comparatively small in number, the data suggest that the placebo response rate is at least as high in this age population.<sup>20,21,29-31</sup> In our study, the exact nature of the high placebo response rate is unclear, but possible factors include frequent follow-up visits, the relatively large number of centers involved (increased variability), and language/cultural factors. Increased visit frequency and the attention associated with these visits may have an intrinsic component of therapy and is different than a "waiting period" control, in which there is no interaction. Furthermore, 8 placebo patients (4.3%) were receiving some form of psychotherapy during the course of the study and 29 (15.7%) had received psychotherapy prior to enrollment, potentially providing these patients with access to previously learned exercises. Thus, randomization to receipt of placebo does not imply complete lack of treatment.

Suicidality is an important concern in depressed patients. [Recently, regulators in the United States and the United Kingdom have issued advisories about the use of paroxetine, another SSRI, in the treatment of children and adolescents with MDD. The FDA is currently reviewing these data and a final determination regarding paroxetine and suicide risk has not yet been reached.] In our sertraline study, the number of suicide attempts was the same in each treatment group (2 for sertraline and 2 for placebo). Our trials showed a lack of significant difference in suicidal ideation between sertraline-treated and placebo patients, as mea-

**Table 3.** Treatment-Emergent Adverse Events in Patients Analyzed for Safety\*

Adverse Events	Sertraline	Placebo
<b>Children†</b>		
Insomnia	17 (19.8)	7 (8.0)
Diarrhea	13 (15.1)	4 (4.5)
Anorexia	9 (10.5)	2 (2.3)
Vomiting	8 (9.3)	4 (4.5)
Agitation	7 (8.1)	2 (2.3)
Urinary incontinence	6 (7.0)	0
Purpura	5 (5.8)	1 (1.1)
<b>Adolescents‡</b>		
Vomiting	8 (7.8)	3 (3.1)
Diarrhea	7 (6.8)	3 (3.1)

\*Data are expressed as No. (%) for events occurring in at least 5% of sertraline-treated patients and with an incidence of at least 2 times that seen in placebo patients.

†For sertraline, n = 86 and for placebo, n = 88.

‡For sertraline, n = 103 and for placebo, n = 96.

sured by the CDRS-R. In patients who continued into the 24-week open-label extension study, only 1 episode of suicidal ideation was reported, and the investigator attributed this event to teasing by classmates. Additionally, the Best Pharmaceuticals for Children Act requires a review of adverse events for a period of 1 year after a drug is granted pediatric exclusivity. This review of sertraline's safety data was recently conducted by the FDA. The agency concluded: "These reports do not provide any safety signals that indicate that the Agency needs to do anything except continue to actively assess the evolving benefit-risk profile of these products [sertraline]."<sup>47</sup> Regardless, it is important to carefully supervise and assess the potential for suicidality in all patients with MDD, and larger studies on this issue should be conducted.

Although our trials were not powered to detect differences by age group, there was some suggestion that sertraline may be more effective in adolescents. Further studies may be helpful to determine whether both age groups respond equally well to drug therapy.

Sertraline appears to be generally well tolerated, although these trials were powered only for efficacy. Patients treated with sertraline more frequently experienced agitation, anorexia, diarrhea, nausea, purpura, urinary incontinence, and vomiting. Although the incidence of dis-

continuations due to adverse events was similar between treatment groups in adolescents, a higher proportion of sertraline-treated children discontinued because of adverse events. The nature of this difference is unclear, although identical dosing regimens were used for both age groups and it is possible that the higher serum levels of sertraline in children<sup>48</sup> resulted in the greater incidence of adverse events. This may suggest a need for reduced initial doses or slower titration of sertraline in children compared with adolescents in an effort to improve tolerability. Regardless of age, careful symptomatic monitoring is warranted in all patients with MDD.

Discontinuation of sertraline was not associated with withdrawal symptoms in either the 10-week double-blind trials or the 24-week open-label extension study. All patients entering the extension study began open-label treatment with 50 mg/d of sertraline, regardless of their dosage in the double-blind study, and no significant untoward reactions were noted as a result of this dosage change.

The clinical importance of the weight difference noted in the 10-week trials is unclear, but in a subset of patients (n=226) who continued into the 24-week open-label extension study, this pattern was reversed and patients previously treated with sertraline displayed a mean weight gain (+2.98 kg) that was greater than in patients previously randomized to placebo (+1.22 kg).<sup>49</sup> Because appetite and weight changes are common in MDD, it is advisable for practitioners to monitor weight patterns in all patients with depression.

Acute studies such as reported here are limited by several factors, including the subjective nature of rating scales and the relatively short duration of treatment exposure. The applicability of these scales to younger patients with less developed insight and ability to form abstract thought is unclear. In addition, most patients were treated with doses of study drug lower than the maximum allowed by the protocol, and it is possible that in a longer-term study,

investigators would have titrated the dosage to higher levels. Although no dose-response relationship for sertraline has been demonstrated, patients who do not respond initially to lower dosages may respond to dosage escalation, up to a maximum of 200 mg/d.

Major depressive disorder is a serious public health problem that is frequently underdiagnosed and inadequately treated.<sup>19</sup> Given the paucity of empirical data available to guide physicians in the psychopharmacological treatment of pediatric MDD, further research is needed. Whether lower initial dosages in children would improve tolerability or long-term sertraline treatment in children and adolescents would result in maintenance of effect and an improvement of quality of life deserves study. Nonetheless, the results reported here support the conclusion that sertraline is an effective, safe, and well-tolerated short-term treatment for children and adolescents with MDD.

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