

# Sertraline in Children and Adolescents With Major Depressive Disorder

CRAIG L. DONNELLY, M.D., KAREN DINEEN WAGNER, M.D., Ph.D., MOIRA RYNN, M.D.,  
PAUL AMBROSINI, M.D., PHYLLIS LANDAU, M.D., RUOYONG YANG, Ph.D.,  
AND CHRISTOPHER J. WOHLBERG, M.D., Ph.D.

## ABSTRACT

**Objective:** To explore time to first response and time to first persistent response of sertraline versus placebo and compare these parameters between children (6–11 years old,  $n = 177$ ) and adolescents (12–17 years old,  $n = 199$ ) with major depressive disorder. **Method:** A 10-week placebo-controlled treatment was followed by a 24-week open-label sertraline treatment. The double-blind studies were not powered to detect efficacy differences between age groups. A post hoc analysis explored time to first response and first persistent response using the Children's Depression Rating Scale-Revised and Clinical Global Impressions-Improvement predefined criteria. **Results:** There were no statistically significant differences in time to first response or first persistent response between sertraline and placebo in children, except for time to first response on Clinical Global Impressions-Improvement. Sertraline had a significantly faster time to first persistent response in adolescents compared to placebo. Within treatment groups, children had a significantly faster time to first response than adolescents, whether treated with placebo or sertraline, but not on time to first persistent response. Both age groups showed similar improvement over 34 weeks of treatment. **Conclusion:** In the double-blind studies, children and adolescents had different patterns of response with sertraline vs. placebo. *J. Am. Acad. Child Adolesc. Psychiatry*, 2006;45(10):1162–1170. **Key Words:** sertraline, major depressive disorder, time to response.

The efficacy and safety of selective serotonin reuptake inhibitors in the short-term treatment of major depressive disorder (MDD) in child and adolescent outpatients was demonstrated in two placebo-controlled studies of fluoxetine (Emslie et al., 1997, 2002), one of

sertraline (Wagner et al., 2003), and one of citalopram (Wagner et al., 2004) and in adolescents 12 to 17 years old in one placebo-controlled study of fluoxetine, cognitive-behavioral therapy, and their combination (March et al., 2004). Currently available evidence of paroxetine is equivocal (Keller et al., 2001), and escitalopram did not demonstrate superiority to placebo (Wagner et al., 2006). Britain's Committee on the Safety of Medicines and the U.S. Food and Drug Administration raised concern regarding the possibility of increased risk of suicidal behavior during treatment with selective serotonin reuptake inhibitors. In a review of 24 pediatric antidepressant trials (Hammad et al., 2006), an analysis of all suicide-related adverse events (AEs; defined as suicidal attempts or ideation) in all drugs, all indications combined showed an overall risk ratio of 1.95 (95% confidence interval [CI] 1.28–2.98, fixed-effects model). The U.S. Food and Drug Administration, following a split vote from an advisory committee, issued a directive to add a black box warning

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Dr. Donnelly is with the Department of Psychiatry, Dartmouth-Hitchcock Medical Center, Lebanon, NH; Dr. Wagner is with the Department of Psychiatry and Behavioral Health Sciences, University of Texas Medical Branch, Galveston; Dr. Rynn is with the Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia; Dr. Ambrosini is with Drexel University Medical School, Philadelphia; and Drs. Landau, Yang, and Wohlberg are with Pfizer Pharmaceuticals Inc., New York.

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Correspondence to Dr. Craig L. Donnelly, Department of Psychiatry, Dartmouth-Hitchcock Medical Center, DHPA One Medical Center Drive, Lebanon, NH 03756; e-mail: craig.l.donnelly@dartmouth.edu.

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describing the increased risk of suicidality in children and adolescents to all antidepressants available in the United States and set out guidelines for careful monitoring of patients taking antidepressants.

Debate over the uniformity of MDD as a diagnosis in children, adolescents, and adults is widespread in the literature (see Kaufman et al., 2001, for review) and has been fueled in part by the findings of differing neurobiological correlates of disease between age groups. Publications to date typically presented efficacy and safety data for children and adolescents combined or adolescents only, but little is known about potential differences in efficacy and safety in the child versus adolescent populations.

The results of a prospectively defined, primary analysis of two identically designed 10-week, double-blind, placebo-controlled trials (Wagner et al., 2003) comparing sertraline and placebo in children and adolescents with MDD, although not powered to detect differences between age groups, suggested that sertraline may be more efficacious in adolescents. At the study endpoint, a slightly greater difference in the Children's Depression Rating Scale-Revised (CDRS-R) mean change between treatment groups was noted in adolescents (sertraline,  $-21.55$  versus placebo,  $-18.20$ ;  $p = .01$ ) than in children (sertraline,  $-24.05$  versus placebo,  $-22.20$ ;  $p = .19$ ; Wagner et al., 2003). Following from these results, this post hoc analysis by age group (children 6–11 years; adolescents 12–17 years) aimed to further explore whether there are any differences in time to first response, time to first persistent response, and selected efficacy and safety parameters between sertraline and placebo, as well as between the age groups. The analyses were based on results of both double-blind studies (Wagner et al., 2003) and an ensuing 24-week open-label extension with sertraline for patients who completed either of the double-blind studies regardless of their degree of improvement or initial group assignment (Rynn et al., 2006).

## METHOD

### Studies

*Study Design.* The analysis was based on the combined results of two identically designed 10-week, placebo-controlled studies and a 24-week, open-label, extension study for patients who completed either of these studies regardless of their degree of improvement or treatment group assignment in the acute study (Rynn et al., 2006; Wagner et al., 2003). Full details of study centers,

inclusion/exclusion criteria, assessment schedule, ethical aspects, and efficacy and safety statistical analyses for double-blind and open-label studies are reported in full detail elsewhere (Rynn et al., 2006; Wagner et al., 2003). The first author of this article (C.L.D.) had unrestricted access to all study data as well as to the results of all post hoc analyses.

*Inclusion and Exclusion Criteria.* Outpatient children (6–11 years) and adolescents (12–17 years) meeting the *DSM-IV* (American Psychiatric Association, 1994) diagnostic criteria for MDD and as determined by the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (Kaufman et al., 1997) for at least 6 weeks duration were eligible for participation. Patients were required to have a CDRS-R score of  $\geq 45$ , indicating at least moderately severe MDD symptomatology (Poznanski and Mokros, 1995), and a Clinical Global Impression of Severity of Illness (CGI-S) rating of  $\geq 4$ , indicating at least a moderate severity of illness.

*Study Medication.* For all patients, treatment was initiated at 25 mg/day for the first 3 days, continuing at 50 mg/day through the end of the second week. Thereafter, in the absence of dose-limiting AEs, the dose could be flexibly titrated upward in increments of 50 mg/day every 2 weeks to a maximum of 200 mg/day, until achieving a satisfactory clinical response. All of the patients entering the open-label study initially received sertraline 50 mg/day followed by the previously described titration. Concomitant psychotropic drug treatment or cognitive-behavioral therapy was not permitted except for chloral hydrate and diphenhydramine intermittently for sleep up to maximum of 1 g and 50 mg per night, respectively.

The prospectively defined primary efficacy parameter was the CDRS-R (Poznanski and Mokros, 1995; Poznanski et al., 1985) Best Description of the Child total score, based on the highest rating for each item across all rating sources (i.e., the child, parent or legal guardian, or others) in the judgment of the investigator. Secondary efficacy parameters were the CGI-Severity (CGI-S) and CGI-I scales (Guy, 1976). Prospectively defined criteria were used in the absence of standard response criteria. CDRS-R responders were patients with a  $\geq 40\%$  decrease (baseline to endpoint) in the adjusted CDRS-R total score, and CGI-I responders with a CGI-I score of  $\leq 2$  ("very much" or "much" improved) at endpoint. Additional secondary efficacy parameters included the total score on the patient-rated Multidimensional Anxiety Scale for Children (March et al., 1997), Children's Global Assessment Scale (CGAS; Shaffer et al., 1983), and Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (Endicott et al., 2006).

The baseline visit for the open-label study was the final visit for the double-blind study. During the open-label study, all of the CDRS-R and CGI ratings were performed during office visits by physician investigators or subinvestigators, also serving as prescribing clinicians.

### Statistical Post Hoc Analyses

Data from the double-blind studies were pooled in a prospectively defined, combined analysis performed on intent-to-treat population (i.e., subjects who took at least one dose of double-blind medication and had any follow-up safety information, baseline and postrandomization efficacy data). An exploratory analysis investigated times to first response and to first persistent response during the double-blind studies using Kaplan-Meier methods. Estimates of the probability of response were plotted over the time from first intake of trial medication to the time first response or first persistent response occurs. First response was the first  $\geq 40\%$  CDRS-R score decrease from baseline, or first postbaseline CGI-I score of 1 or 2. First

persistent response was the first  $\geq 40\%$  CDRS-R score postbaseline decrease and no decrease  $< 40\%$  after that time, or the first postbaseline CGI-I score of 1 or 2 and no increases  $> 2$  after that time. As exploratory analyses, both Wilcoxon test and log-rank test results were reported from Kaplan-Meier analyses. Wilcoxon scores, which emphasize differences during the earlier phase of a study, were used to detect any difference between response curves at the beginning of the trial and log-rank scores, which emphasize differences during the latter phases of a study, were used to detect any difference between response curves towards the end of the study. All Kaplan-Meier analyses were performed separately for children and adolescents, as well as comparisons between children and adolescents within treatment groups of sertraline and placebo.

Further post hoc analyses compared the endpoint dose of sertraline (using *t* test), total number of dropouts, dropouts because of AEs, and subjects with any AEs (Fisher exact test), changes from baseline in the CDRS-R scores (the interaction between age group and treatment effect) between the sertraline-treated children and adolescents. Full details of primary/secondary efficacy and safety outcome parameters statistical analyses were described elsewhere (Rynn et al., 2006; Wagner et al., 2003).

## RESULTS

Eighty-six children and 103 adolescents were randomized to sertraline, and 91 and 96, respectively, to placebo. The respective numbers in the intent-to-treat group were 84 and 101 for sertraline, and 87 and 92 for placebo. Of the 299 patients completing the double-blind studies, 46 were from 13 sites not participating in the extension study, and 27 patients decided not to participate. Of 226 enrolled patients (109 children, 117 adolescents), 221 were treated with medication, 216 (106 children, 110 adolescents) were included in the open-label intent-to-treat population, and 62 children and 76 adolescents completed the open-label study.

### Patient Characteristics

Baseline characteristics are detailed in Table 1. No significant differences were noted between treatment groups. A greater percentage of sertraline-treated adolescents were female, whereas proportionately more male children were randomized to placebo.

At the double-blind baseline, the mean CGI-S and CDRS-R total scores suggested moderately severe to severe symptomatology across treatment and age groups (Table 1). From week 3 onward, the mean daily doses of both sertraline and placebo equivalents were substantially higher in the adolescent compared with the children groups and in the placebo compared to the sertraline groups (double-blind study endpoint: adolescents, sertraline 133.8 mg/day; placebo 142.6; children, sertraline

102.0, placebo 128.0; open-label study endpoint: adolescents 120.8 mg/day, children 98.4 mg/day).

### Time to First Response and First Persistent Response During Double-Blind Treatment

*Children.* There were no significant differences between sertraline- and placebo-treated children in time to first response on CDRS-R (Fig. 1A). A statistically significant difference favoring sertraline- over placebo-treated children was present across both the earlier and later weeks of therapy in the time to first response on CGI-I (Wilcoxon test on treatment differences at the beginning,  $p = 0.049$ ; and log-rank test on treatment differences at the end of the study,  $p = .034$ ).

There were no significant differences between sertraline- and placebo-treated children in time to first persistent response on CDRS-R (Fig. 1B) and CGI-I (Wilcoxon test on treatment differences at the beginning of the study,  $p = .154$ ; and log-rank test on treatment differences at the end of the study,  $p = .204$ ).

*Adolescents.* Sertraline-treated adolescents had a similar time to first response on CDRS-R (Fig. 1A) and statistically significantly faster time to first response on CGI-I at the beginning of the study (Wilcoxon test,  $p = .027$ ) compared to the placebo-treated adolescents.

Time to first persistent response statistically significantly favored sertraline over placebo both in the earlier and later weeks of therapy on CDRS-R (Fig. 1B) and CGI-I (Wilcoxon test,  $p = .022$ ; log-rank test,  $p = .014$ ).

*Children Versus Adolescents.* Children had significantly faster time to first response than adolescents as measured by CDRS-R, whether treated with sertraline (Wilcoxon test,  $p = .009$ ; log-rank test,  $p = .002$ ) or placebo (Wilcoxon test,  $p = .053$ ; log-rank test,  $p = .020$ ). Similar results were obtained on the CGI-I (sertraline, Wilcoxon test,  $p = .001$ ; log-rank test,  $p = .009$ ; placebo, Wilcoxon test,  $p = .011$ ; log-rank test,  $p = .016$ ).

There were no significant differences between children and adolescents in time to first persistent response as measured by CDRS-R (sertraline, Wilcoxon test,  $p = .248$ ; log-rank test,  $p = .246$ ; placebo, Wilcoxon test,  $p = .120$ ; log-rank test,  $p = .067$ ) or CGI-I (sertraline, Wilcoxon test,  $p = .359$ ; log-rank test,  $p = .322$ ; placebo, Wilcoxon test,  $p = .072$ ; log-rank test,  $p = .097$ ).

In the sertraline group, the estimated median time of first response on the CDRS-R was 15 days in children (95% CI 14–21) and 22 days in adolescents (95% CI 20–28) and of the first persistent response it was 28 days

**TABLE 1**  
Baseline Characteristics

	Children				Adolescents			
	Sertraline		Placebo		Sertraline		Placebo	
	Male (n = 43)	Female (n = 43)	Male (n = 56)	Female (n = 35)	Male (n = 38)	Female (n = 65)	Male (n = 47)	Female (n = 49)
Double-Blind Studies								
Age, yr, mean (SD)	8.9 (1.5)	9.1 (1.5)	9.3 (1.4)	9.0 (1.5)	14.0 (1.4)	14.6 (1.7)	14.4 (1.5)	14.7 (1.5)
Weight, kg, mean (SD)	38.2 (15.6)	38.8 (16.4)	39.5 (13.4)	34.2 (9.1)	62.8 (21.9)	60.6 (15.2)	67.9 (23.3)	56.2 (15.2)
Height, cm, mean (SD)	137.2 (11.4)	138.9 (13.8)	139.8 (10.8)	136.4 (9.0)	162.7 (13.7)	159.8 (9.4)	168.7 (11.0)	156.9 (11.1)
Primary diagnosis								
MDD, single episode, n/N (%)	82/86 (95)		86/91 (95)		89/103 (86)		75/96 (78)	
Mean duration of illness since first diagnosis, mo	21.6		17.1		22.6		21.4	
MDD, recurrent, n/N (%)	4/86 (5)		5/91 (5)		14/103 (14)		21/96 (22)	
Mean duration of illness since first diagnosis, mo	35.3		45.0		46.1		38.6	
CDRS-R Total Score	62.0 (11.2)		63.5 (9.8)		66.2 (10.6)		65.6 (12.0)	
CGI-S score	4.5 (0.6)		4.5 (0.6)		4.7 (0.6)		4.6 (0.7)	
	Children				Adolescents			
	Sertraline <sup>a</sup>		Placebo <sup>a</sup>		Sertraline <sup>a</sup>		Placebo <sup>a</sup>	
	Male (n = 16)	Female (n = 28)	Male (n = 43)	Female (n = 22)	Male (n = 20)	Female (n = 36)	Male (n = 36)	Female (n = 25)
Open-label extension								
Age, yr, mean (SD)	9.4 (1.6)	9.4 (1.7)	9.6 (1.6)	9.7 (1.1)	14.4 (1.5)	14.9 (1.8)	14.5 (1.6)	14.8 (1.6)
CDRS-R Total, mean (SD)	32.6 (13.2)		38.3 (13.7)		37.0 (15.0)		40.9 (15.4)	
CGI-S Score, mean (SD)	2.6 (1.3)		3.0 (1.2)		2.8 (1.2)		3.2 (1.4)	

Note: MDD = major depressive disorder, CDRS-R = Children's Depression Rating Scale-Revised; CGI-S = Clinical Global Impressions-Severity of Illness Scale.

<sup>a</sup> Initial assignment; all subjects in open-label study received sertraline.

in children (95% CI 22–45) and 32 days in adolescents (95% CI 25–49). In the placebo group, the respective times of first response were 21 days in children (95% CI 17–23) and 23 days in adolescents (95% CI 21–29) and of first persistent response 28 days in children (95% CI 22–45) and 32 days in adolescents (95% CI 25–49).

#### Efficacy Results

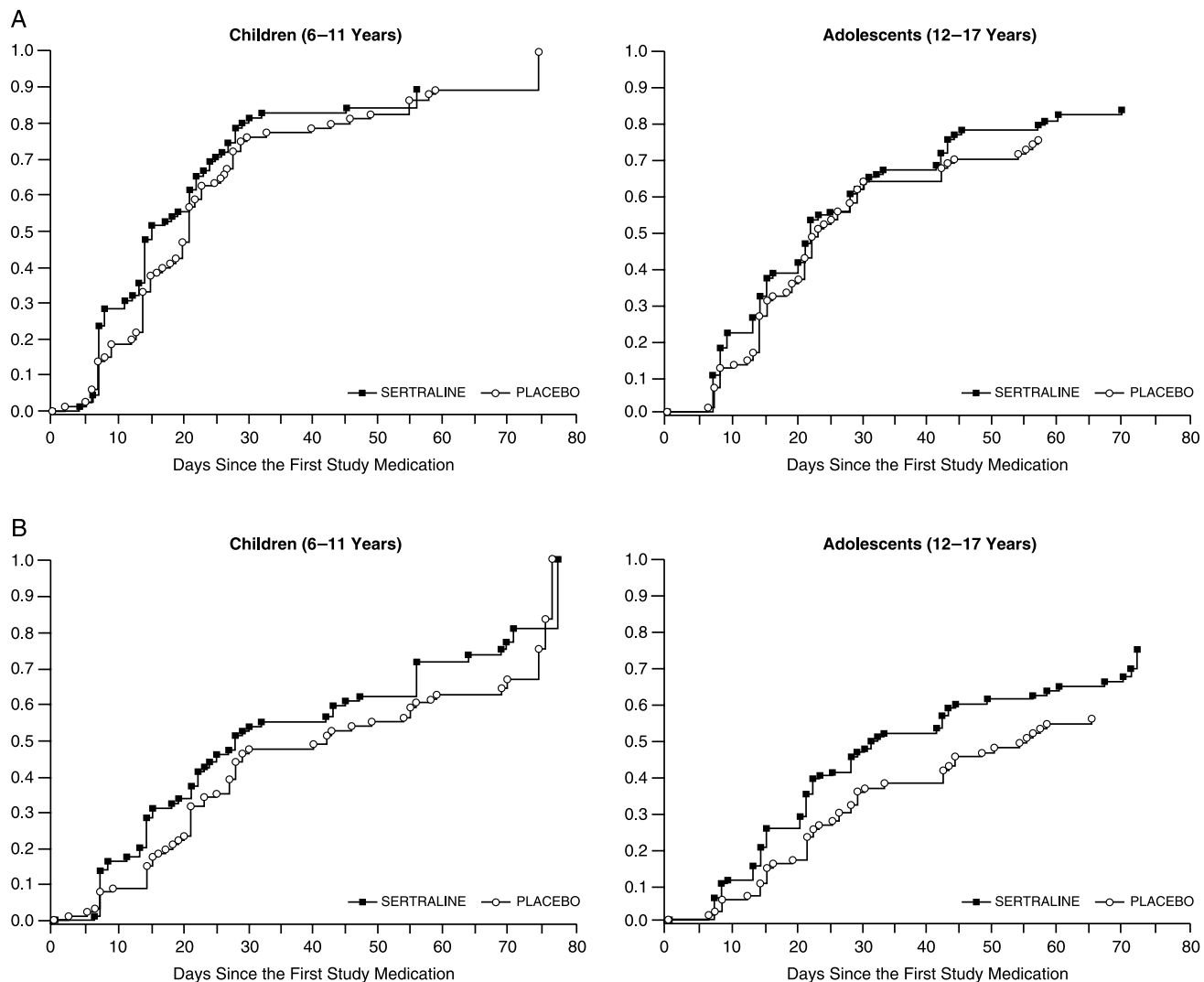
Changes from baseline in the primary and secondary efficacy parameters per age group during the double-blind and open-label studies are presented in Table 2. Although the studies were not powered to detect differences between age groups, some results favored sertraline-treated adolescents, but not children, over placebo at the

end of the double-blind studies. However, both age groups improved equally at the open-label endpoint.

#### Safety

**Double-Blind Studies.** Overall discontinuation rates were 27.9% (24/86) among sertraline-treated and 10.2% (9/88) among placebo-treated children. For adolescents, the rates were similar for both sertraline (21.4%, 22/103) and placebo (19.8%, 19/96). However, the difference between sertraline-treated children and adolescents was not significant ( $p = .3198$ ).

Among the sertraline-treated children 15.1% (13/86) discontinued because of an AE compared to none of the



**Fig. 1** Kaplan-Meier analysis of time to first and first persistent response on Children's Depression Rating Scale-Revised (CDRS-R) and Clinical Global Impressions Scale (CGI) in children and adolescents during up to 10 weeks of double-blind treatment with either sertraline or placebo. A, Time to first response on CDRS-R. B, Time to first persistent response on CDRS-R.

placebo-treated children (0/88). By contrast, the proportions among adolescents were similar (sertraline: 3.8% [4/103] and placebo: 4.1% [4/96]). The difference between percentages of sertraline-treated children and adolescents discontinuing because of AEs was statistically significant ( $p = .0096$ ).

Among children, discontinuations started at the outset of treatment and appeared related to the protocol-allowed sertraline dose increments. By contrast, discontinuations among adolescents occurred in the second half of the study, starting from week 6. In the sertraline group, the proportions of subjects with at least one AE were generally higher in children than in

adolescents; however, the difference was not statistically significant ( $p = .4747$ ).

Four of the seven serious AEs occurring in the sertraline group and one of the six serious AEs in the placebo group were in children. Suicide-related events were reported in seven subjects: three children (two suicidal ideation, one suicide attempt) and two adolescents (one suicidal ideation, one suicide attempt) in the sertraline group and no children and two adolescents (both suicide attempts; one patient attempted twice) in the placebo group. Body weight decreased by  $\geq 7\%$  in 7.1% sertraline-versus 0.0% placebo-treated children and in 1.9% versus 1.1% of adolescents, respectively. Overall mean change in

**TABLE 2**  
Efficacy Results

Double-Blind Studies Endpoint	Children			Adolescents		
	Sertraline [n], Mean (SE) <sup>a</sup>	Placebo [n], Mean (SE) <sup>a</sup>	<i>p</i> <sup>b</sup>	Sertraline [n], Mean (SE) <sup>a</sup>	Placebo [n], Mean (SE) <sup>a</sup>	<i>p</i> <sup>b</sup>
CDRS-R Total Score, <sup>c</sup> mean change	[84], -24.05 (1.05)	[87], -22.20 (1.01)	.192	[101], -21.55 (0.95)	[92], -18.20 (0.99)	.012
CGI-Severity <sup>c</sup> [n], mean change (SD)	[84], -1.32 (0.08)	[87], -1.10 (0.08)	.042	[101], -1.13 (0.07)	[91], -0.92 (0.08)	.047
CGI-I <sup>c</sup> [n], mean change (SD)	[84], 2.45 (0.08)	[87], 2.65 (0.08)	.074	[101], 2.66 (0.07)	[92], 2.86 (0.08)	.052
CDRS Responder, <i>n/N</i> , %	62/86, 72.6%	61/91, 66.7%	.387	66/101, 65.4%	47/92, 51.1%	.037
CGI-I responders, <i>n/N</i> , %	56/86, 65.5%	54/91, 59.8%	.365	61/101, 60.4%	42/92, 45.7%	.043
CGAS <sup>d</sup>	[78], 15.81 (1.50)	[78], 16.84 (1.50)	.627	[87], 16.16 (1.42)	[85], 12.73 (1.44)	.091
MASC <sup>d</sup>	[76], -5.54 (1.71)	[78], -4.01 (1.69)	.341	[86], -5.54 (1.61)	[85], -2.95 (1.61)	.255
PQ-LES-Q <sup>d</sup>	[77], 8.00 (1.01)	[77], 7.30 (1.00)	.617	[86], 4.86 (0.95)	[85], 2.11 (0.96)	.040
Open-Label Study Endpoint	Children [n], Mean (SE)		<i>p</i> <sup>e</sup>	Adolescents [n], Mean (SE)		<i>p</i> <sup>e</sup>
CDRS-R Total Score <sup>f</sup>	[106], -35.5 (2.59)		<0.001	[110], -34.2 (1.66)		<0.001
CGI-Severity <sup>f</sup>	[106], -2.5 (0.12)		<0.001	[110], -2.3 (0.13)		<0.001
CGI-Improvement <sup>g</sup>	[106], 1.6 (0.90)		<0.001	[110], 1.8 (1.06)		<0.001
CGAS <sup>f</sup>	[92], 24.1 (1.48)		<0.001	[101], 21.3 (1.45)		<0.001
MASC <sup>f</sup>	[89], -6.4 (2.07)		0.003	[100], -8.5 (1.66)		<0.001
PQ-LES-Q <sup>f</sup>	[90], 5.6 (1.13)		<0.001	[99], 7.3 (1.09)		<0.001

Note: CDRS-R = Children’s Depression Rating Scale-Revised; CGI-S = Clinical Global Impressions-Severity of Illness Scale; CGI-I = Clinical Global Impressions-Improvement Scale; CGAS = Children’s Global Assessment Scale; MASC = Multidimensional Anxiety Scale for Children; PQ-LES-Q = Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire.

<sup>a</sup> Or as otherwise indicated.

<sup>b</sup> CDRS-R, CGI-I, and CGI-S: *p* values from test of least-squares means, mixed model analyses sertraline versus placebo treatment groups. CGAS, MASC, and PQ-LES-Q: *p* value from *t* test, analysis of covariance model.

<sup>c</sup> Least-squares mean and SE from repeated measures, mixed model with age category, site, treatment, treatment by age, and week-by-treatment age category interaction as fixed effects, and patient as the random effect. Baseline CDRS-R or CGI-S score used as a covariate.

<sup>d</sup> Adjusted mean change from baseline to endpoint using analysis of covariance model.

<sup>e</sup> *p* Value for open-label study from one-sample *t* test.

<sup>f</sup> Mean change from double-blind baseline to open-label endpoint (last observation carried forward).

<sup>g</sup> Open-label mean endpoint value.

body weight in children was -0.17 kg with sertraline versus 0.98 kg with placebo and -0.55 kg versus 0.61 in adolescents. Full details regarding the AEs per age group occurring at a rate of at least 5% and at least twice the incidence in placebo-treated patients and serious AEs are described in full detail elsewhere (Wagner et al., 2003).

*Open-Label Extension Study.* Only 7.5% (8/107) children and 6.2% (7/114) adolescents discontinued because of AEs. Of the three serious AEs, two occurred in children (suicidal ideation and pneumonia) and one in an adolescent (upper respiratory infection). One adolescent discontinued as a result of moderately increased liver function tests (aspartate transaminase), attributed by the investigator to sertraline. As expected with usual growth among children and adolescents,

more patients gained weight (children, an increase of ≥7% in 29.1% and a decrease of ≥7% in 1.0%; adolescents, an increase of ≥7% in 25.2% and a decrease of ≥7% in 0.9%). Full details regarding the AEs per age group occurring at a rate of at least 5% and at least twice the incidence in placebo-treated patients are described in full detail elsewhere (Rynn et al., 2006).

**DISCUSSION**

To our knowledge, this is the first study exploring time to response in child and adolescent outpatients with MDD during 10 weeks of double-blind, placebo-controlled treatment with sertraline. The results of our analyses suggest that time to first response appeared to

be significantly faster in children treated with sertraline compared to placebo (on CGI) and in children compared to adolescents irrespective of whether they were treated with sertraline or placebo (on both CDRS-R and CGI). The time to first persistent response was significantly faster in sertraline- compared to placebo-treated adolescents, with no differences between children and adolescents treated with either sertraline or placebo. Further significant improvements in primary and secondary efficacy parameters at open-label endpoint compared to double-blind endpoint in both children and adolescents imply that improvement of depressive symptoms continued over the open-label phase, thus suggesting potential further benefit from treatment beyond the initial 10 weeks. However, the removal of the placebo arm during the open-label treatment may have influenced the results, considering that patients, parents, and investigators knew at that point that the active treatment was administered.

Sertraline was generally well tolerated over 34 weeks of treatment, although significantly more children from the outset discontinued because of AEs. The reasons may be, at least in part, the result of an aggressive up-titration scheme or a too-high initial dose. Moreover, the endpoint dose in adolescents was significantly higher than in children. Thus, tolerability may have been improved by a more conservative dosing schedule for younger patients, in terms of a lower initial dose, lower dose increments, and a longer period between dose increments. The majority of patients in both groups demonstrated stable age-related weight patterns throughout the extension study. When it occurred, weight loss tended to be exhibited early during the double-blind treatment phase.

Suicide-related events were reported in a total of seven subjects during the double-blind studies and in one subject during the open-label study. In the double-blind studies, the events in children occurred between days 21 and 46, with all subjects receiving 100 mg/day sertraline at the time of the event. The events involving adolescents occurred at days 49 and 50, with a 100- and 150-mg/day dose of sertraline. During the extension study, the event occurred at day 155 with sertraline 200 mg/day. An environmental precipitant was present in two sertraline-treated subjects (one adolescent and one child), one placebo-treated child during the double-blind study, and in one child during the open-label study. No relationship could be

established in either children or adolescents between the suicidality-related events and recent dose escalation or any prodromal AEs.

#### Limitations

It is unclear why the time to response to sertraline in our study showed different patterns in children and adolescents. A statistically significantly faster attainment of persistent response in sertraline- compared to placebo-treated adolescents on both CDRS-R and CGI-I may suggest the observed improvements could be caused by a true antidepressant response, previously described in adults with MDD (Quitkin et al., 1987). By contrast, the lack of differentiation in children may indicate that observed improvements are, at least partially, the result of the influence of nonspecific, nonmedication-related therapeutic factors playing a role in a double-blind study, especially in prepubertal children. In our study, first response occurred earlier in children than in adolescents, irrespective of whether they were treated with sertraline or placebo. However, it is unclear whether this finding is due to a true drug effect or, again, is the result of nonspecific therapeutic factors that children may be more sensitive to in comparison to adolescents. In our analysis, first response to sertraline in children occurred after a median of  $\geq 2$  weeks and of first persistent response after a median of  $\geq 4$  weeks of treatment. In adolescents, first response to sertraline appears to occur after a median of  $\geq 3$  weeks and first persistent response after a median of  $\geq 4.5$  weeks, respectively. It should be, however, noted that the results of all exploratory analyses need to be interpreted with caution.

Although the double-blind studies were not powered to detect differences between age groups, advantages in the CDRS-R and CGI-I responder rates and changes in PQ-LES-Q in adolescents at double-blind endpoint extend the previous observation by Wagner et al. (2003) and are similar to results of another study demonstrating the efficacy of the selective serotonin reuptake inhibitor fluoxetine in adolescent MDD (March et al., 2004), thus suggesting sertraline may be more effective in adolescents than in children. Furthermore, in our exploratory analyses, CGI-I response rates in adolescents at the double-blind study endpoint (sertraline 60.4%, placebo 45.7%;  $p = .043$ ) were similar to those obtained in placebo-controlled, short-term, double-blind studies of sertraline in adult MDD population (sertraline 61.1%, placebo 38.3%;  $p$  value not reported [Reimherr

et al., 1990]; sertraline 55%, placebo 37%;  $p = .016$  [Lydiard et al., 1997]).

Although placebo response was high in both age groups, it was particularly pronounced in children (CDRS-R response rate: sertraline 72.6%, placebo 66.7%,  $p = .387$ ; CGI-I response rate: sertraline 65.5%, placebo 59.8%,  $p = .365$ ) versus adolescents (CDRS-R response rate: sertraline 65.4%, placebo 51.1%,  $p = .037$ ; CGI-I response rate: sertraline 60.4%, placebo 45.7%,  $p = .043$ ). MDD is known to be a highly placebo-responsive illness in acute studies of children and adolescents, with placebo response rates ranging from 20% to 80% (Birmaher et al., 1998; Emslie et al., 1997; Geller et al., 1992; Kowatch et al., 1999). High placebo rates observed in children in our study further suggest nonmedication-related factors may have played an important role in this population. It is also possible that the results were influenced by the site selection and variables such as the number of sites, their nature (i.e., academic or private practice), and the expertise of the staff (Emslie et al., 2005). For example, in the fluoxetine study performed in a single academic medical center, the difference between the active compound and placebo in the percentage of patients with CGI scores 1 or 2 was 27% (Emslie et al., 2005), whereas in our study the difference was 5.7% in children and 14.7% in adolescents.

It is also unclear why adolescents tolerated treatment with sertraline better than children, although our results concur with a recent report suggesting children are more vulnerable than adolescents to activation AEs or vomiting (Safer and Zito, 2006). In our study dosing was equal in both age groups, but considering the lower mean body weight and volume of distribution, the starting dose may have been too high or up-titration too rapid in children. Thus, tolerability and/or compliance may have been decreased, and discontinuation rates resulting from AEs increased. In addition, sertraline was shown to have greater  $C_{max}$  and  $AUC_{0-24}$  in children compared to adolescents with MDD or obsessive-compulsive disorder, but these differences disappeared after parameters were normalized for body weight (Alderman et al., 1998). In the Alderman et al. study, sertraline was well tolerated in both children and adolescents, with adverse experiences similar to those previously reported by adult patients. Although pharmacokinetic testing was not used in the present studies, similar results could likely have been obtained.

## Clinical Implications

In our analysis, sertraline was associated with different patterns of response in children and adolescents, suggesting that the early response seen in children may not be persistent in nature, whereas in adolescents, once the response to sertraline occurs, it tends to persist. Furthermore, duration of treatment with sertraline beyond 10 weeks may be an important factor in clinical response in children and adolescents with MDD and may bring about a greater likelihood of response, particularly in younger patients. Because MDD at all ages is associated with an increased risk of suicidal and self-injurious behavior, all MDD patients require close observation for the emergence of suicidality. This study also suggests that for the treatment of MDD, children may require somewhat lower initial doses of sertraline as well as a slower upward titration. Also, children may be more likely to stop treatment because of the emergence of medication-induced side effects. Clinicians may thus choose to initiate treatment at lower doses and titrate the dose of sertraline more slowly in children while paying particular attention to both counseling about and monitoring for the emergence of side effects, especially early in treatment. Finally, the different patterns of response to and tolerability of sertraline in children and adolescents seen in our analysis deserve further investigation.

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**Pain Assessment for Pediatric Patients in the Emergency Department** Amy L. Drendel, DO, MS, David C. Brousseau, MD, MS, Marc H. Gorelick, MD, MSCE

**Objective:** To examine the relationship between pediatric patient visit characteristics and pain score documentation in the emergency department (ED) and determine whether documentation of a pain score is associated with increased analgesic use. **Methods:** A cross-sectional analysis was conducted of ED visits for pediatric patients from the National Hospital Ambulatory Medical Care Survey (1997–2000). Survey weighted regression first was used to assess the association between patient visit characteristics and pain score documentation. The regression then was repeated to determine the association between documentation of a pain score and analgesic use, adjusting for visit characteristics. **Results:** A total of 24,707 visits were included. Only 44.5% of visits had documented pain scores. In the regression analysis, younger age, self-pay, visits to pediatric facilities, and visits that were not designated as injury related were associated with decreased pain score documentation. Documentation of pain score was associated with increased odds of an analgesic prescription and opioid prescription. When no pain score was documented, the odds of receiving any analgesic was similar to visits with pain documented as mild. **Conclusion:** ED pain score documentation is suboptimal in the pediatric population. Infants and toddlers are at particular risk for not having a pain score documented. There is a significant association between pain score documentation and the use of any analgesic, particularly opioids. Improvements in pain documentation for acutely ill and injured children are needed to improve pain management. **Pediatrics** 2006;117:1511–1518.