Fluoxetine for Acute Treatment of Depression in Children and Adolescents: A Placebo-Controlled, Randomized Clinical Trial

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ABSTRACT

Background: This report presents results from the acute treatment phase of a clinical trial designed to confirm efficacy of a fixed dose of 20 mg of fluoxetine in children and adolescents with major depressive disorder (MDD). **Method:** After a 3-week screening period, 122 children and 97 adolescents with MDD (*DSM-IV*) were randomly assigned to placebo or fluoxetine. After a 1-week placebo lead-in, fluoxetine-treated patients received fluoxetine 10 mg/day for 1 week, then fluoxetine 20 mg/day for 8 weeks. **Results:** Fluoxetine was associated with greater mean improvement in Children's Depression Rating Scale-Revised (CDRS-R) score than placebo after 1 week ($p < .05$) and throughout the study period. Significantly more fluoxetine-treated patients (41%) met the prospectively defined criteria for remission than did placebo-treated patients (20%) ($p < .01$). More fluoxetine- (65%) than placebo-treated (53%) patients met the prospectively defined response criterion of ≥30% decrease in CDRS-R score, but this difference was not significant ($p = .093$). Significantly more fluoxetine- than placebo-treated patients completed acute treatment ($p = .001$). There were no significant differences between treatment groups in discontinuations due to adverse events ($p = .408$). **Conclusion:** Fluoxetine 20 mg daily appears to be well tolerated and effective for acute treatment of MDD in child and adolescent outpatients. Fluoxetine is the only antidepressant that has demonstrated efficacy in two placebo-controlled, randomized clinical trials of pediatric depression. *J. Am. Acad. Child Adolesc. Psychiatry*, 2002, 41(10):1205–1215. **Key Words:** fluoxetine, major depressive disorder, selective serotonin reuptake inhibitor.

Depression occurs in approximately 2% of children and 4% to 8% of adolescents (American Academy of Child and Adolescent Psychiatry [AACAP], 1998), with major depressive disorder (MDD) being twice as prevalent in adolescent girls as in adolescent boys (Emslie et al., 1990). Children and adolescents with depression are at increased risk for school failure and dropout (Simeon, 1989) and for suicide (Brent, 1993; Levy et al., 1992; Pfeffer et al., 1991). Age at time of recognition of first depressive episode appears to be decreasing (Kovacs and Gastonis, 1994); this finding suggests that many individuals experience their first episodes of depression as children or adolescents.

Much has been written about the use of antidepressants in children with various mood and anxiety disorders, but there have been few adequately powered controlled clinical trials in the area of MDD. Controlled studies of tricyclic antidepressant treatment for children and adolescents with depression failed to produce a replicable pattern of efficacy (Geller et al., 1999). In a controlled, double-blind clinical trial, venlafaxine was not superior to placebo for treatment of depression in children and adolescents (Mandoki et al., 1997).

For first-line acute treatment of MDD in children and adolescents, the AACAP recommends psychotherapy, treatment with a selective serotonin reuptake inhibitor

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(SSRI), or both combined, depending on the patient, the patient's circumstances, and the severity of disease. SSRIs are recommended because of their relative safety, low lethality on overdose, and ease of administration (AACAP, 1998). The Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder recommends using fluoxetine, paroxetine, or sertraline first when medication is warranted for child and adolescent MDD (Hughes et al., 1999).

In an open-label trial, sertraline appeared to be efficacious for the treatment of MDD in patients between 12 and 20 years of age (Ambrosini et al., 1999). However, this finding has not yet been confirmed in a placebo-controlled, double-blind clinical trial. Paroxetine was reported to be effective for the treatment of MDD in children and in adolescents in an open-label trial (Rey-Sanchez et al., 1997). Paroxetine was also statistically significantly superior to placebo on one of two primary efficacy measures in a controlled clinical trial of treatment for adolescents (but not children) with MDD (Keller et al., 2001).

Efficacy of fluoxetine in the treatment of pediatric depression has been demonstrated in a double-blind, placebo-controlled study (Emslie et al., 1997). This study demonstrated that a fixed dose (20 mg/day) of fluoxetine was efficacious and well tolerated. Other reports have indicated that children and adolescents may require fluoxetine doses greater than 20 mg/day (Colle et al., 1994; Jain et al., 1992; Simeon et al., 1990). One naturalistic study indicated that doses less than 20 mg may be effective for some adolescents (Boulos et al. 1992).

This report presents safety and efficacy data from the 9-week acute treatment phase of a clinical trial designed to confirm and extend the findings of previous studies of fluoxetine in children and adolescents with MDD. Disease-specific and broad-based efficacy measures were evaluated. The safety of fluoxetine treatment was assessed by examining treatment-emergent solicited and nonsolicited adverse events and vital signs.

METHOD

Study Design

A multiphase study was designed to examine efficacy and tolerability of various dosing strategies for fluoxetine treatment of depressed children and adolescents. The initial phase, reported here, was designed to confirm a previous report that fluoxetine 20 mg was effective and well tolerated for acute treatment of pediatric MDD.

To obtain the most reliable assessment of patients' condition, this study incorporated an extensive diagnostic evaluation period requiring three independent diagnostic interviews (visits 1, 2, and 3 [week –3, –2, and –1]). The Diagnostic Interview for Children and Adolescents (DICA) (or the Missouri Assessment of Genetics Interview for Children [MAGIC], which incorporates it) was administered to all enrolled patients and their parents at each interview, to establish the diagnosis of MDD. (Only the questions present in both the DICA and MAGIC were used for this study.) The interviews were conducted by three different interviewers, at least one of whom was a psychiatrist. Other interviewers were qualified and experienced pediatric health care professionals. Each interviewer had access to information from previous interviews for each patient. This was done to ensure the accuracy and completeness of the information gathered during the evaluation process. Final diagnoses were determined after visit 3. Patients and their parent(s) or guardian(s) were interviewed separately. To increase interrater reliability, interviewers received training in the use of the DICA or MAGIC. No drug was administered during the evaluation period. This was followed by a single-blind, 1-week, placebo lead-in period (between visits 3 and 4 [week –1 and week 0]). Patients who responded during this period (defined as ≥30% decrease in Children's Depression Rating Scale-Revised [CDRS-R] or a Clinician's Global Impressions [CGI] Improvement score of 1 or 2) were discontinued from the study. Those who did not respond during the placebo lead-in were assigned to treatment groups by means of a computer-generated randomization sequence. Randomization was stratified by gender and age category across investigative sites.

Patients in the placebo treatment group were instructed to take three capsules, which contained placebo, once daily for 9 weeks. Patients in the fluoxetine treatment group were also instructed to take three capsules daily. For the first week, these consisted of two placebo capsules and a capsule containing 10 mg of fluoxetine. For weeks 2 through 9, one capsule contained placebo and two capsules contained 10 mg of fluoxetine each.

After receiving study medication, patients returned for efficacy and adverse event assessments at weeks 1, 2, 3, 5, 7, and 9 (visits 5 through 10).

Participants

Eligibility requirements for participation in the trial included primary diagnosis of nonpsychotic MDD (single or recurrent) as defined by *DSM-IV* criteria and depressive symptoms of at least moderate severity as defined by a CDRS-R total score >40 and a CGI-Severity rating of ≥4. All other inclusion and exclusion criteria are shown in Table 1.

This study was conducted by 15 investigators throughout the United States. Study sites included academic hospitals and private research psychiatric clinics. Patients were recruited from site patient populations, as well as by newspaper and radio advertising, with the goal of achieving a trial population with a wide range of severity of MDD. This study was conducted and informed consent was obtained according to the ethical principles stated in the Declaration of Helsinki, the applicable guidelines for good clinical practice, and the applicable laws and regulations of the United States. An informed consent document approved by the investigational review board (IRB) for each site was signed by patients' parents or guardians. Patients may have also provided consent or assent depending on the requirements of each site's IRB.

Measurements and Procedures

Data were collected at week –3 and at each patient visit by clinicians who were blinded to treatment group. Patients were assessed by patient and parent report at each visit using the CDRS-R and CGI-Severity scales, administered by qualified personnel. At each visit except visit 1 (week –3), patients were also assessed with the CGI-Improvement scale. Adverse event data were collected by two meth-

TABLE 1
Inclusion and Exclusion Criteria

Patients were included in the study only if they met all of the following criteria:
- Male and female outpatients
- Children (aged 8 to <13 years) and adolescents (aged 13 to <18 years) at the time of study entry
- A primary psychiatric diagnosis of nonpsychotic major depressive disorder (single or recurrent) as defined by the *DSM-IV* criteria
- Depressive symptoms of at least moderate severity as defined by a CDRS-R total score >40 and a CGI-Severity rating of moderate or greater
- Able to swallow whole medication without difficulty
- No clinically significant laboratory findings in hematology, chemistry, and urinalysis at study entry based on the judgment of the investigator
- ECG without clinically significant abnormalities; clinical significance was determined by investigator and physician interpreting the ECG
- Educational level and degree of understanding so that the patients and parents could communicate intelligibly with the investigator and study coordinator; normal intelligence based on the judgment of the investigator
- Patients and parents judged to be reliable who agreed to keep appointments for clinic visits and all tests and examinations required by the protocol

Patients were excluded from the study for any of the following reasons:
- Investigators and their immediate families were not permitted to be subjects or patients
- Persons who had previously completed or withdrawn from this study
- Females who were pregnant, breastfeeding or who were sexually active and were not using medically accepted means of contraception
- Serious illness (including cardiac, hepatic, renal, respiratory, endocrinological, neurological, or hematological disease) that was not stabilized so that hospitalization for treatment of that illness was likely within the next 2 months
- Patients with abnormal thyroid function
- Seizure disorder with a seizure occurring within the past 6 months, except for febrile seizures
- Diagnosis of any of the following *DSM-IV*–defined disorders: bipolar I or II disorder, sleep-wake disorder, psychotic depression (lifetime), anorexia (lifetime), bulimia (lifetime), borderline personality disorder, or substance abuse disorder (within the past 6 months)
- Patients with one or more first-degree relatives with bipolar I disorder
- Organic brain diseases
- Persons whose illness has previously failed to respond to adequate antidepressant treatment (at least 8 weeks' treatment within the typical maximum adult therapeutic range)
- Serious suicidal risk
- History of severe allergies, multiple adverse drug reactions, or known allergy to the study drug
- Receipt of an investigational drug within 30 days prior to study entry
- Receipt of any behavior-altering, centrally acting, or excluded medication within 7 days prior to study entry
- Documented hypersensitivity to fluoxetine
- Prior adequate treatment with fluoxetine (12 weeks on a fixed dose of 20 mg or greater)
- Receipt of fluoxetine within 3 months prior to study entry
- Regular use of other psychotropic or centrally acting drugs, including lithium and the psychostimulants (i.e., drugs normally prescribed for depression, mania, anxiety, insomnia, attention-deficit/hyperactivity deficit disorder, or psychosis) within 2 weeks prior to study entry
- Use of neuroleptics during the 2 weeks prior to study entry or of depot neuroleptics within the 6 weeks prior to study entry
- Use of an MAOI within 2 weeks (14 days) prior to study entry or potential need to use an MAOI within 5 weeks of discontinuation of treatment
- Use of tryptophan, St. John's wort, or melatonin within 2 weeks prior to study entry
- Potential need for the continuation or initiation of other treatments for depression, including cognitive-behavioral therapy and behavioral therapy, except for supportive therapy on an individual or family basis

Note: CDRS-R = Children's Depression Rating Scale-Revised; CGI-Severity = Clinician's Global Impressions-Severity scale; ECG = electrocardiogram; MAOI = monoamine oxidase inhibitor.

ods. At visits 2 (week –2) through 10 (week 9), adverse events were collected after general inquiry at the beginning of each visit. Events reported by patients at this time are referred to as "nonsolicited" adverse events. At the end of visits 4 (baseline) through 10 (week 9), adverse events were collected by asking patients about specific symptoms listed on the Side Effects Checklist. These are referred to as "solicited" adverse events. An event was considered treatment-emergent if it was new or increased in severity after baseline.

The following instruments were used to capture efficacy and adverse events:

The CDRS-R (Poznanski and Mokros, 1996), a clinician-rated scale used as a screening and diagnostic tool and a measure of sever-

ity of depression in children, consists of 17 items scored from 1 to 5 or 1 to 7 (minimum score = 17).

CGI-Severity (Guy, 1976) is a 7-point clinician-rated scale that measures the severity of a patient's symptoms.

CGI-Improvement (Guy, 1976) is a 7-point clinician-rated scale that measures change in global patient condition from baseline.

The Hamilton Anxiety Rating Scale (HAMA) (Hamilton, 1959) is a clinician-rated scale that measures the severity of anxiety; it consists of 14 items, each scored 0 to 4.

The Beck Depression Inventory (BDI) (Beck and Steer, 1984), a patient-rated scale, assesses major symptom categories associated with depression. Scores range from 0 to 62. The BDI was completed only by the adolescents (aged 13 to <18 years) in this study.

The Children's Depression Inventory (CDI) (Kovacs, 1985) is a patient-rated scale based on the BDI, which measures the severity of depression in children. Scores range from 0 to 54. The CDI was completed only by the children (aged 8 to <13 years) in this study.

The Global Assessment of Functioning Scale (GAF) (Endicott et al., 1976) is a clinician-rated instrument that assesses the patient's current and highest level of functioning. Scores range from 1 to 90 (90 indicates good functioning in all areas).

The Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) is a clinician-rated scale that assesses depressive symptoms. The MADRS is not commonly used as a measure of depression for children and adolescents and was included as an exploratory assessment.

Nonsolicited adverse events were captured regardless of relationship to study medication, as actual terms and were categorized using the *Coding Symbols for Thesaurus of Adverse Reaction Terms* (U.S. Food and Drug Administration, 1995) by blinded clinical personnel and verified by a blinded physician.

The Side Effects Checklist (Emslie et al., 1997) is a 30-item symptom checklist based on the Subjective Treatment Emergent Symptoms Scale developed by the National Institute of Mental Health. Asked if they had been bothered by or had trouble with any of the items on the scale, patients could choose from the following responses: "not at all," "just a little," "pretty much," "very much," or "I don't know."

Other safety measures, including laboratory tests and electrocardiograms (ECGs), were performed at a later stage of this study and are not reported here.

Statistical Analyses

Sample size was designed to detect a 20% difference between fluoxetine 20 mg and placebo in the proportion of patients meeting protocol-defined response criteria with approximately 80% power and a .05 significance level (two-sided). The primary efficacy measure was the CDRS-R response rate. Response rate was prospectively defined as a ≥30% decrease in CDRS-R total score from week 0 to endpoint (last patient visit, weeks 2 to 9). Remission was defined as an endpoint CDRS-R total score of ≤28. Analyses of response and remission included only those patients treated at least 2 weeks with study drug. Thus only fluoxetine-treated patients who had received at least 1 week of treatment with 20 mg of fluoxetine were included. All other analyses, including mean change in CDRS-R from baseline to endpoint and weekly analyses, were intent-to-treat/last patient observation carried forward. Secondary measures included changes in CDRS-R subscores and CGI-Severity from baseline to endpoint. For analysis of CGI-Improvement, only endpoint values were compared, since this scale inherently measures total improvement in direct comparison with a patient's condition at baseline.

A repeated-measures analysis of variance (ANOVA) was performed on the CDRS-R total score. The baseline and each postbaseline visit were included in the model as the dependent variables. The initial model for this analysis included treatment, visit (within-subject factor), treatment by visit interaction, investigator, and investigator by treatment interaction with an unstructured within-subject variance-covariance matrix. If the investigator by treatment interaction was not statistically significant ($p \geq .1$), it was dropped from the model.

Adverse events were analyzed by comparing the incidence of treatment-emergent nonsolicited adverse events between treatment groups. Weeks –3 to –1 were defined as baseline for nonsolicited adverse events. Treatment-emergent solicited adverse events from the Side Effects Checklist were compared between treatment groups using week 0 as baseline. An adverse event was considered treatment-emergent if it first occurred or worsened after baseline. Changes in vital signs from baseline to endpoint were compared between fluoxetine and placebo treatment groups.

The Fisher exact test was used to compare percentages. An ANOVA (type III sums of squares) with the term treatment in the model was used when comparing change scores or endpoint scores between treatments. Treatment by subgroup interactions were assessed for children versus adolescents, males versus females, and patients who had a family history of depression versus patients who did not. To test for a treatment by subgroup interaction on mean change, an ANOVA with treatment, sub-

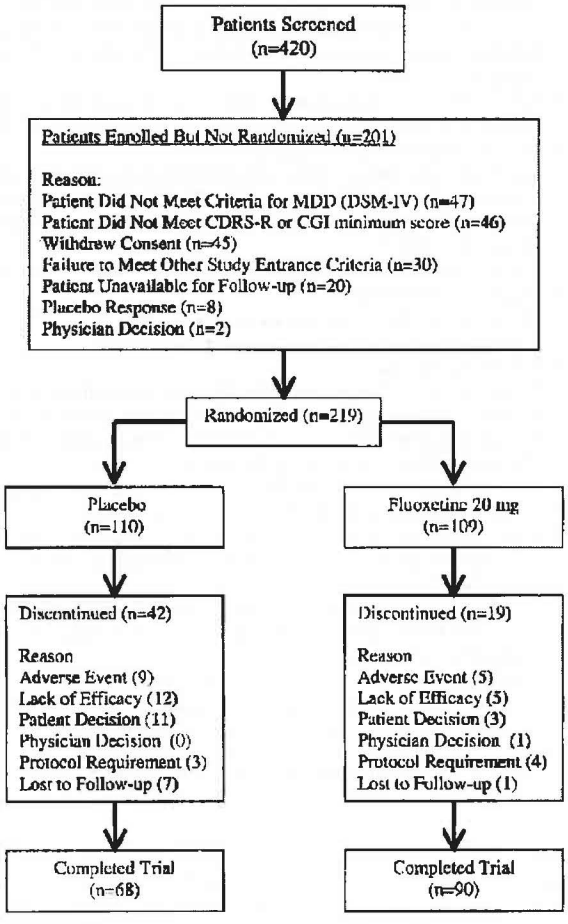

Fig. 1 Flow diagram showing patient disposition. MDD = major depressive disorder; CDRS-R = Children's Depression Rating Scale-Revised; CGI = Clinician's Global Impressions.

group, and the treatment by subgroup interaction in the model was performed. For response and solicited treatment-emergent adverse events, a Breslow-Day test for the homogeneity of odds ratios across subgroups was performed. For nonsolicited treatment-emergent adverse events, comparisons between treatments were made within subgroups.

All tests of hypotheses were considered statistically significant if the two-sided p value was less than .05. No adjustments for multiple comparisons were made.

RESULTS

Baseline Patient Comparisons

After 2 weeks of evaluation, and a 1-week placebo lead-in period, 109 patients were randomly assigned to fluoxetine treatment and 110 to placebo treatment (Fig. 1). There were no statistically significant differences between treatment groups in patient demographics at baseline (Table 2). Randomization of patients resulted in treatment groups that were reasonably balanced for the current comorbid conditions attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, and bipolar II disorder. (Patients with bipolar II disorder above threshold level were excluded from the trial.) There was less balance between groups for conduct disorder. The fluoxetine and placebo treatment groups contained three patients and one patient with conduct disorder, respectively. They also contained 5 and 16 patients with subthreshold conduct disorder, respectively.

Mean baseline scores on the CGI-Severity scale indicated patients had moderate to marked severity of illness.

TABLE 2
Patient Demographics

	Fluoxetine (n = 109)	Placebo (n = 110)	p-Value
Ethnicity, n (%)			.071[a]
White	96 (88.1)	84 (76.4)	
Asian	1 (0.9)	0	
African American	6 (5.5)	8 (7.3)	
Hispanic	3 (2.8)	10 (9.1)	
Other	3 (2.8)	8 (7.3)	
Age (years), mean ± SD	12.70 ± 2.46	12.69 ± 2.67	.983[b]
Age category, n (%)			1.00[a]
8–<13 years old	61 (56.0)	61 (55.5)	
13–<18 years old	48 (44.0)	49 (44.5)	
Gender, n (%)			1.00[a]
Female	54 (49.5)	54 (49.1)	
Male	55 (50.5)	56 (50.9)	
Age at onset of depression, mean ± SD	10.41 ± 2.92	10.26 ± 3.11	.715[b]
Duration of current episode (weeks)			
Mean	60.44	61.29	.936[b]
Range	4–572	2–450	
First episode of depression, n (%)	87 (79.8)	86 (78.2)	.868[a]
Current comorbid conditions, n (%)			
Bipolar II disorder			
Absent	108 (99.1)	109 (99.1)	1.00[a]
Subthreshold	1 (0.9)	1 (0.9)	
Present	0	0	
Attention-deficit/hyperactivity disorder			
Absent	73 (67.0)	68 (61.8)	.551[a]
Subthreshold	20 (18.3)	27 (24.5)	
Present	16 (14.7)	15 (13.6)	
Oppositional defiant disorder			
Absent	71 (65.1)	69 (62.7)	.905[a]
Subthreshold	21 (19.3)	24 (21.8)	
Present	17 (15.6)	17 (15.5)	
Conduct disorder			
Absent	101 (92.7)	93 (84.5)	.020[a]
Subthreshold	5 (4.6)	16 (14.5)	
Present	3 (2.8)	1 (0.9)	

[a] p Value derived using Fisher exact test.
[b] p Value derived using a type III sum of squares analysis of variance with treatment in the model.

Patients were required to have at least moderate severity of illness (score of 4) to be enrolled in this trial. Patients were also required to have CDRS-R scores above 40, the cut point for depression. The mean baseline scores of 55.1 to 57.1 are well above this cut point.

BDI and CDI scores were not among the criteria for enrollment in this trial, and mean baseline scores on both of these self-report measures were unexpectedly low. Although mean baseline BDI scores for adolescents were above the cut point for major depression (Roberts et al., 1991), mean baseline CDI scores for children were below the cut point for depression (Silverman and Rabian, 1999). Given the high percentage of patients in this study who had comorbid ADHD, it may not be surprising that results of the clinician-rated measures were not reflected by the results of the patient-rated scales.

Efficacy

Compared with placebo, fluoxetine treatment was associated with significantly greater improvement in CDRS-R after 1 week of treatment and for the remainder of the study (Fig. 2). Fluoxetine-treated patients had significantly greater mean change in CDRS-R score at endpoint than did placebo-treated patients ($p < .001$) (Table 3). The 95% confidence interval for the difference between treatment groups in mean change in CDRS-R is completely above zero, indicating that there is a 95% or greater probability that fluoxetine is superior to placebo in improvement on CDRS-R score. Traditionally, an effect size of 0.2 is considered to be small, 0.5 medium, and 0.8 large (Cohen, 1988). In the repeated-measures model, there was a significant treatment by visit interaction ($p < .001$) indicating treatment course over time differed for the two treatment groups. The overall treatment effect was also statistically significant ($p = .006$), as was the comparison of change from baseline to endpoint between the treatment groups ($p = .003$).

There was no significant therapy by subgroup interaction for mean change in CDRS-R based on age category ($p = .371$), gender ($p = .632$), or family history of depression ($p = .493$). Significantly more fluoxetine-treated patients (41.3%) than placebo-treated patients (19.8%) met the prospectively defined criteria for remission ($p < .01$).

Mean improvement in CDRS-R mood and behavior subscores was also significantly greater for fluoxetine-treated patients than for placebo-treated patients at weeks 1 through 9 ($p < .05$). For the CDRS-R somatic and sub-

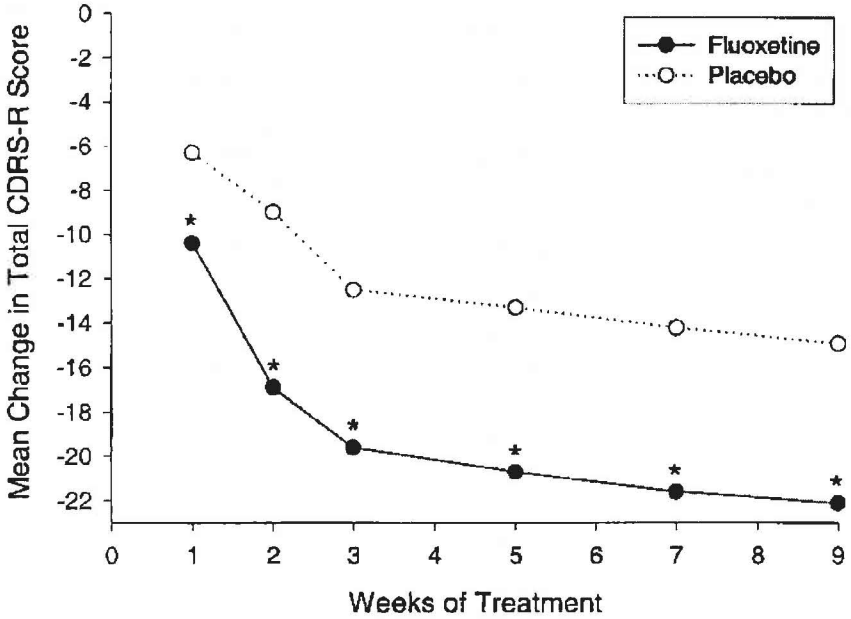

Fig. 2 Mean change from baseline for fluoxetine- and placebo-treated patients on the Children's Depression Rating Scale-Revised (CDRS-R) (last observation carried forward). Asterisks indicate p values (analysis of variance): $^*p < .05$.

TABLE 3
Change From Baseline to Endpoint in CDRS-R, MADRS, HAMA, GAF, and CGI-Severity Scales

	Fluoxetine[a]		Placebo[b]		Differences in Mean Change[c]		Effect
	Baseline	Endpoint	Baseline	Endpoint	(95% CI)	*p* Value[d]	Size
CDRS-R	57.1 ± 9.9	35.1 ± 13.5	55.1 ± 11.8	40.2 ± 13.5	7.1 (3.3 to 10.9)	<.001	0.51
MADRS	21.6 ± 7.5	11.2 ± 9.0	21.5 ± 8.3	13.9 ± 8.2	2.8 (0.4 to 5.2)	.023	0.31
HAMA	10.2 ± 5.2	5.4 ± 4.7	11.0 ± 5.8	7.4 ± 5.2	1.2 (–0.3 to 2.6)	.115	0.22
GAF	53.3 ± 6.7	64.8 ± 12.4	54.6 ± 7.1	63.9 ± 9.8	–2.2 (–1.0 to 5.4)	.176	0.20
CGI-Severity	4.5 ± 0.6	2.9 ± 1.2	4.4 ± 0.6	3.4 ± 1.1	0.6 (.3 to 1.0)	<.001	0.54

Note: Values represent mean ± SD. CDRS-R = Children's Depression Rating Scale-Revised; MADRS = Montgomery-Asberg Depression Rating Scale; HAMA = Hamilton Anxiety Rating Scale; GAF = Global Assessment of Functioning; CGI-Severity = Clinician's Global Impressions–Severity scale; CI = confidence interval.

[a] For CDRS-R, MADRS, and CGI-Severity, $n = 109$; for HAMA, $n = 106$; and for GAF, $n = 104$.

[b] For CDRS-R and MADRS, $n = 105$; for HAMA, $n = 94$; for GAF, $n = 86$; and for CGI-Severity, $n = 106$.

[c] Difference in Mean Change shows results of subtracting the mean change in the fluoxetine treatment group from the mean change in the placebo treatment group. 95% confidence intervals for the differences are shown in parentheses below. If the entire 95% confidence interval is greater than zero, this indicates a 95% or greater probability that the mean change associated with fluoxetine treatment is greater than the mean change associated with placebo.

[d] *p* Value for difference in mean change between treatment groups, derived using a type III sum of squares analysis of variance with treatment in the model.

jective subscores, fluoxetine was significantly superior to placebo at weeks 2, 5, 7, and 9 and weeks 2, 3, 7, and 9, respectively ($p < .05$).

Response was prospectively defined as a 30% or greater improvement in CDRS-R score. By this definition, the difference in the percentage of patients responding to treatment (fluoxetine: 65.1%; placebo: 53.5%) was not significant ($p = .093$) (Table 4A). No significant difference in response rates was observed among subgroups based on age category ($p = .629$), gender ($p = .897$), or

TABLE 4
Number (and Percentage) of Patients Meeting Possible Definitions of Response

Calculation Method Value[a]	Response Criteria	Fluoxetine ($n = 109$)	Placebo ($n = 101$)	*p*
A. $\frac{\text{Baseline} - \text{Endpoint}}{\text{Baseline}}$[b]				
	≥20%	88 (80.7)	62 (61.4)	.002
	≥30%	71 (65.1)	54 (53.5)	.093
	≥40%	55 (50.5)	29 (28.7)	.002
	≥50%	37 (33.9)	17 (16.8)	.007
	≥60%	17 (15.6)	5 (5.0)	.013
	≥70%	5 (4.6)	0	.060
B. $\frac{(\text{Baseline} - 17) - (\text{Endpoint} - 17)}{\text{Baseline} - 17}$[c]				
	≥20%	95 (87.2)	69 (68.3)	.001
	≥30%	86 (78.9)	62 (61.4)	.006
	≥40%	77 (70.6)	56 (55.4)	.031
	≥50%	63 (57.8)	41 (40.6)	.014
	≥60%	56 (51.4)	29 (28.7)	.001
	≥70%	40 (36.7)	21 (20.8)	.015

[a] Fisher exact test.

[b] Original method of calculating response rate.

[c] Response rate calculation that corrects for the nonzero minimum score on the Children's Depression Rating Scale-Revised.

family history of depression ($p = .809$). A comparison of results with response defined over a range from ≥20% to ≥70% reduction in CDRS-R score (Table 4A) indicates fluoxetine would be significantly superior to placebo if response had been defined as ≥20%, ≥40%, ≥50%, or ≥60% reduction in CDRS-R total score.

Half of all fluoxetine-treated patients (52.3%) were rated much or very much improved (CGI-Improvement score of 1 or 2) compared with about a third of placebo-treated patients (36.8%, $p = .028$). Fluoxetine-treated patients also had significantly greater improvement in CGI-Severity score than did placebo-treated patients ($p < .001$) (Table 3). There was no significant therapy by subgroup interaction for mean CGI-Improvement score based on age category ($p = .959$), gender ($p = .379$), or family history of depression ($p = .290$).

Mean improvement in HAMA score was not significantly different between fluoxetine- and placebo-treated patients (–4.8 ± 5.2 and –3.7 ± 5.2, respectively; $p = .115$). The finding that the 95% confidence interval of the difference between treatment groups in mean change in HAMA score spans zero confirms that the two treatment groups did not separate significantly on mean improvement in HAMA score. Fluoxetine-treated patients showed significantly greater improvement than placebo-treated patients in CGI-Severity and MADRS scores, but not GAF score (Table 3). The effect size for fluoxetine is medium for the CGI-Severity scale, but small for the GAF scale. There were no significant differences between treatment groups in improvement in BDI score (fluoxetine: –4.6 ± 8.2; placebo: –5.3 ± 7.8; $p = .700$) or CDI score (fluoxetine: –2.4 ± 9.0; placebo: –2.8 ± 6.8; $p = .822$).

Safety

Headache was the only nonsolicited adverse event reported significantly more often by fluoxetine-treated patients than by placebo-treated patients ($p = .017$). Of interest, there was no significant difference between treatment groups in the number of patients reporting headaches on the Side Effects Checklist ($p = .273$). No items on the checklist occurred significantly more often in the fluoxetine treatment group, although trouble with paying attention ($p = .088$) and with dizziness ($p = .092$) trended in that direction. The only statistically significant difference between treatment groups was for trouble pronouncing words ($p = .015$), which was associated with placebo. No clinically relevant treatment differences in solicited or nonsolicited treatment-emergent adverse events were observed among subgroups based on age category, gender, or family history of depression during the 9 weeks of this study.

One fluoxetine-treated patient and four placebo-treated patients experienced serious adverse events during the 9-week treatment period. Two patients experienced serious adverse events requiring hospitalization, but they did not leave the study: a fluoxetine-treated patient experienced swollen tonsils and a placebo-treated patient experienced abdominal pain and appendicitis. Three patients, all receiving placebo, experienced adverse events requiring hospitalization and causing them to discontinue their participation in the study (kidney infection, aggressive behavior, and self-mutilatory behavior).

Ninety (82.6%) fluoxetine- and 68 (61.8%) placebo-treated patients completed the 9-week study period. This difference was significant ($p = .001$). There was no significant difference between treatment groups for any individual discontinuation reason, although there was a trend toward significance for patient decision (fluoxetine: 3 patients [2.8%]; placebo: 11 patients [10.0%]; $p = .050$) and loss to follow-up (fluoxetine: 1 patient [0.9%]; placebo: 7 patients [6.4%]; $p = .065$). One fluoxetine-treated patient (0.9%) and no placebo-treated patients discontinued because of physician decision ($p = .498$). Four fluoxetine-treated patients (3.7%) and three placebo-treated patients (2.7%) discontinued because of protocol requirements ($p = .721$).

There was no significant difference between the fluoxetine and placebo treatment groups in discontinuations due to lack of efficacy (5 [4.6%] and 12 [10.9%] patients, respectively; $p = .128$) or adverse events (5 [4.6%] and 9 [8.2%] patients, respectively; $p = .408$). Eleven patients discontinued because of nonserious adverse events. Among placebo-treated patients, one each discontinued for rash, abdominal pain, alopecia, anxiety, dizziness, and headache (a total of six patients). Among fluoxetine-treated patients, one each discontinued for rash, agitation, constipation, hyperkinesia, and manic reaction (a total of five patients). Throughout the 9 weeks of acute treatment, one fluoxetine-treated patient (0.9%) experienced manic reaction. No placebo-treated patients experienced manic reaction, but this difference between treatment groups was not statistically significant.

There were no statistically significant differences between treatment groups for changes from baseline in vital signs, including sitting heart rate, sitting systolic blood pressure, sitting diastolic blood pressure, or temperature. Other safety measures, including laboratory tests and ECGs, were performed at a later phase of this study and will be included in future reports.

DISCUSSION

Fluoxetine was well tolerated and effective in a double-blind, placebo-controlled study evaluating 9 weeks of acute therapy with fluoxetine 20 mg daily in 219 child and adolescent outpatients with MDD. Fluoxetine 20 mg daily was more effective than placebo for the treatment of depression as demonstrated by significantly greater improvement in the CDRS-R score. During the first week of treatment, fluoxetine-treated patients received 10 mg of fluoxetine daily. Since fluoxetine was statistically significantly superior to placebo within 1 week, it is possible that 10 mg daily may be an effective dose for MDD in some young patients. Further study is necessary to confirm this finding.

Fluoxetine was associated with statistically significantly greater improvement at endpoint in all four CDRS-R subscores than was placebo. Fluoxetine was also significantly superior to placebo on global measures of improvement (CGI-Improvement) and disease severity (CGI-Severity). Significantly more fluoxetine-treated than placebo-treated patients met remission criteria at endpoint.

A statistically significantly greater number of fluoxetine-treated patients than placebo-treated patients had CDRS-R score improvements of greater than or equal to 20%, 40%, 50%, or 60%. The same was not true at 30% ($p = .093$).

A review of the literature using CDRS-R as a measure of treatment effectiveness indicates that a standard definition of response for CDRS-R does not exist. Many studies examined mean change in CDRS-R and did not use a predefined threshold of improvement to categorize patients as responders or reactors (Bernstein et al., 2000; Emslie et al., 1997; Ghaziuddin et al., 1996; Mandoki et al., 1997; Weisz et al., 1997).

Rintelmann and colleagues (1996) used a 20% or greater improvement in CDRS-R to define a patient population they called "reactors." Examination of the data suggests differences in how percentages were calculated between that study and this one. Our original calculations did not correct for the fact that the CDRS-R has a minimum score of 17, not 0. We used the formula: percent change equals (baseline score – endpoint score)/baseline score. Rintelmann and colleagues appear to have used a formula that does correct for the nonzero minimum score of the CDRS-R: percent change equals ([baseline score – 17] – [endpoint score – 17])/(baseline score – 17). That formula is likely to be a better method of assessing change than the one used in the prospective definition of response for this study. For instance, using our original method, a patient with an initial score of 45 at baseline with maximal improvement at endpoint (a CDRS-R score of 17) would have a calculated percentage improvement of 62%. Using the formula of Rintelmann and colleagues, the fact that this patient had achieved the maximum possible improvement would be reflected by a calculated percentage improvement of 100%. If the formula of Rintelmann and colleagues is used to calculate the percentage change in CDRS-R from the data of this study, statistically significantly more fluoxetine-treated patients than placebo-treated patients had CDRS-R scores that decreased ≥20%, ≥30%, ≥40%, ≥50%, ≥60%, and ≥70% ($p < .05$) (Table 4B).

All study patients met *DSM-IV* criteria for MDD; however, the study population contained a larger percentage of patients with low BDI and CDI scores than might be expected among American youths with MDD. (Roberts and colleagues [1991] reported that approximately 84% of high school students with current MDD and 20% of high school students without current MDD will score above the cut points of 11 for girls and 15 for boys.) The reason for the comparatively low BDI and CDI scores in our study population is unclear. It is possible that the reading levels of these measures—third to fifth grade for the CDI and eighth grade for the BDI—as well as the fact that one third of our study population had comorbid ADHD, may have played a role. The low baseline scores for these measures suggest that changes in these scores may not have been an accurate assessment of change in depressive condition for this patient group. Because the initial scores were low, it is not surprising that there were no statistically significant differences between treatment groups in improvement on CDI and BDI scores during this study. These results are similar to those reported previously (Emslie et al., 1997).

Assessment by MADRS was included in this study as an exploratory measure. The mean changes in MADRS score in this study are consistent with the mean changes in CDRS-R scores. Further study is necessary to determine the true validity of MADRS as a measure of depressive symptoms in children and adolescents.

This report contains data from the first phase of a longer clinical trial. Laboratory and ECG tests were performed at baseline, at 19 weeks and at 51 weeks, but not during the 9-week fixed-dose phase of the trial reported here. Those data will be reported in full in subsequent reports.

Throughout this study period, fluoxetine 20 mg/day was well tolerated by children and adolescents; significantly fewer fluoxetine- than placebo-treated patients discontinued their participation in the study. Only one nonsolicited adverse event (headache) was reported significantly more often by fluoxetine-treated patients than by patients receiving placebo. No solicited adverse event occurred more often in fluoxetine-treated patients than in placebo-treated patients. This is consistent with the safety profile observed for fluoxetine in treatment of obsessive-compulsive disorder in children and adolescents (Geller et al., 2001).

Limitations

Patients who enrolled in this study were predominantly white. While no significant differences between whites and nonwhites were observed, the number of nonwhites was too small to conclude that fluoxetine efficacy and safety are constant across ethnic groups. Information about patients' socioeconomic status was not collected during this trial; therefore, we cannot conclude that fluoxetine efficacy and safety were constant across socioeconomic groups.

Clinical Implications

The present study is the second randomized, controlled, double-blind clinical trial of fluoxetine for acute treatment of children and adolescents with MDD. The efficacy and safety results, consistent with those of an earlier clinical trial (Emslie et al., 1997), indicate fluoxetine 20 mg is a well-tolerated and effective treatment for depression in children and adolescents.

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