Escitalopram in the Treatment of Adolescent Depression: A Randomized Placebo-Controlled Multisite Trial

GRAHAM J. EMSLIE, M.D., DANIEL VENTURA, PH.D., ANDREW KOROTZER, PH.D., AND STAVROS TOURKODIMITRIS, PH.D.

ABSTRACT

Objective: This article presents the results from a prospective, randomized, double-blind, placebo-controlled trial of escitalopram in adolescent patients with major depressive disorder. **Method:** Male and female adolescents (aged 12–17 years) with *DSM-IV*–defined major depressive disorder were randomly assigned to 8 weeks of double-blind treatment with escitalopram 10 to 20 mg/day (n = 155) or placebo (n = 157). The primary efficacy parameter was change from baseline to week 8 in Children's Depression Rating Scale–Revised (CDRS-R) score using the last observation carried forward approach. **Results:** A total of 83% patients (259/312) completed 8 weeks of double-blind treatment. Mean CDRS-R score at baseline was 57.6 for escitalopram and 56.0 for placebo. Significant improvement was seen in the escitalopram group relative to the placebo group at endpoint in CDRS-R score (−22.1 versus −18.8, p = .022; last observation carried forward). Adverse events occurring in at least 10% of escitalopram patients were headache, menstrual cramps, insomnia, and nausea; only influenza-like symptoms occurred in at least 5% of escitalopram patients and at least twice the incidence of placebo (7.1% versus 3.2%). Discontinuation rates due to adverse events were 2.6% for escitalopram and 0.6% for placebo. Serious adverse events were reported by 2.6% and 1.3% of escitalopram and placebo patients, respectively, and incidence of suicidality was similar for both groups. **Conclusions:** In this study, escitalopram was effective and well tolerated in the treatment of depressed adolescents. *J. Am. Acad. Child Adolesc. Psychiatry,* 2009;48(7):721–729. **Key Words:** depression, treatment, SSRI. Clinical trial registration information—The Safety and Efficacy of Escitalopram in Pediatric Patients With Major Depressive Disorder. URL: *http://www.clinicaltrials.gov*. Unique identifier: NCT00107120.

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Correspondence to Graham J. Emslie, M.D., University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd. Dallas, TX 75390-8589; e-mail: graham.emslie@utsouthwestern.edu.

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Major depressive disorder (MDD) is a frequent and serious disorder in adolescents and often leads to significant impairments in school, work, and family and peer relationships. Despite increased public and professional awareness, depression in adolescents frequently goes unrecognized and untreated.[1] Treatment of depression ranges from supportive management to specific therapies (e.g., cognitive-behavioral therapy and interpersonal therapy) and antidepressants. Treatment choice depends on multiple factors, such as severity, psychosocial stressors, patient and parent or guardian preference, and course of illness, to name a few.

Guidelines for treatment of pediatric depression have recently been published for pediatricians and child and adolescent psychiatrists in North America[2–4] and psychiatrists in the United Kingdom.[5] Common factors

in all guidelines are adequate assessment (diagnosis), prospective monitoring of efficacy and safety, brief active monitoring before initiating specific treatments, and antidepressants and/or specific therapies for moderate-to-severe depression.

A meta-analysis of recent randomized controlled trials (RCTs) of antidepressants included 13 trials of pediatric MDD with 2,910 participants and involved both selective serotonin reuptake inhibitors (SSRIs) and non-SSRIs. The overall effect size for pediatric MDD was 0.25, with the number needed to treat of 10. These outcomes were based on overall absolute response rates of 61% for antidepressants and 50% for placebo. The overall rate of suicidal ideation and attempts for all antidepressant trials was 3% for antidepressants and 2% for placebo, giving a number needed to harm of 112, a positive benefit-risk ratio.[6] In terms of individual antidepressants, there are three positive trials of fluoxetine,[7–9] one for citalopram,[10] and a positive pooling of two trials for sertraline.[11]

In evaluating safety in clinical trials, specifically the definitions of suicidality, the Food and Drug Administration contracted with an independent team of experts from Columbia University to develop more specific definitions for suicidal behavior. In particular, a goal was to differentiate suicide attempts with at least some intent to die and self-injurious behavior with no intent.[12] The new classification system was used to retrospectively review and recategorize suicide-related behaviors in all pediatric antidepressant trials, and the analyses showed an increase in suicidality with antidepressants compared with placebo. Contrary to the results shown with adverse event reporting, clinician-rated suicidality (based on single items from depression severity scales) showed no differences between antidepressants and placebo.[13]

In a recent study of depressed children and adolescents, escitalopram, which is the therapeutically active enantiomer of racemic citalopram, did not show evidence of efficacy over placebo. However, in the subset of the adolescent participants (aged 12–17 years; n = 157), escitalopram appeared to be more effective than placebo in reducing depressive symptom severity and improving global functioning.[14] With the limited number of available effective antidepressants for adolescent depression, and only one antidepressant with a Food and Drug Administration indication, additional research into the efficacy and safety of escitalopram is warranted, particularly given its potential effect in adolescents. The study presented is the second RCT of escitalopram in depressed youth and compares escitalopram with placebo in adolescents (aged 12–17 years). This study prospectively assessed suicidality using the Modified Columbia Suicide Severity Rating Scale (MC-SSRS) and collected clinician and self-report measures specific to suicidal ideation and behaviors.

METHOD

This was a randomized, double-blind, placebo-controlled trial that was conducted from April 2005 to May 2007 at 40 sites in the United States. The trial was approved by the institutional review board for each study center. Patients were required to provide assent, and the patient's parent or legal guardian had to provide written consent before the conduct of any study-specific procedures. A parent or caregiver capable of providing information about the patient's condition had to accompany the patient at all study visits.

This study was sponsored by Forest Laboratories, the makers of escitalopram, with agreements between the sponsor and investigative sites regarding the collection, submission, and dissemination of the results. The sponsor ran all statistical analyses. The article was drafted by the manuscript authors (G.E.: "Introduction" and "Discussion"; A.K.: "Method" and "Results"). Several meetings with the sponsor and authors to request additional data analyses were held, and all authors provided iterative revisions to the article before submission.

Patients

The study enrolled male and female outpatients who were between 12 and 17 years of age, inclusive, at the initial (screening) visit. The patients met diagnostic criteria for MDD, as defined by the *DSM-IV*, with the duration of the current MDD episode of at least 12 weeks at screening. Diagnosis was established at screening by agreement of two independent clinicians through the use of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version,[15] a semistructured diagnostic interview that assesses the major diagnostic criteria relevant to psychiatric disorders in children and adolescents, including depression. In addition, the patients were required to have a score of at least 45 on the Children's Depression Rating Scale-Revised (CDRS-R)[16,17] at both the screening and baseline visits and a score of at least 4 on the Clinical Global Impressions-Severity (CGI-S) Scale[18] at baseline. Additional inclusion criteria were a score of 80 or higher on the Kaufman Brief Intelligence Test at screening and normal physical examination, laboratory tests, and electrocardiogram (ECG) results at screening.

The patients who were excluded were those who had a principal diagnosis meeting *DSM-IV* criteria for an Axis I disorder other than MDD; or who currently met *DSM-IV* criteria at screening for attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, posttraumatic stress disorder, bipolar disorder, pervasive developmental disorder, mental retardation, conduct disorder, or oppositional defiant disorder; or who had any psychotic features or a history of any psychotic disorder, as defined by *DSM-IV* (other comorbid Axis I diagnoses were allowed if they were not the primary disorder); or any personality disorder of sufficient severity to interfere with participation in the study (as judged by the investigator). Similarly, patients with a history of a manic or hypomanic episode or

seizures or a history within the past year of anorexia nervosa, bulimia, or substance abuse or dependence (including alcohol) were excluded. Patients with a first-degree relative with bipolar disorder were not enrolled. Patients considered a suicide risk by the investigator, including those who had active suicidal ideation, had made a suicide attempt, or had ever been hospitalized because of a suicide attempt, were also not eligible for the study.

Patients were excluded for a positive test for alcohol or other prohibited medication on the urine drug screen at screening (or during the second visit). Patients were required to have not been treated with any antidepressant or anxiolytic medication within 2 weeks of baseline (4 weeks for fluoxetine), any neuroleptic or stimulant within 6 months of screening, or any investigational drug within 30 days or 5 half-lives before screening. Patients who had been in a previous clinical study of citalopram or escitalopram, who had a history of hypersensitivity reaction to any SSRI, or who had previously failed to respond to an adequate trial of escitalopram or citalopram or to adequate trials of two other SSRIs were excluded. Concomitant treatment with certain prescription or over-the-counter medications (including any psychotropic drugs other than zolpidem or zaleplon for insomnia) was prohibited. Pregnant women or nursing mothers were excluded, as were female subjects of childbearing potential not practicing a reliable birth control method. Initiation of psychotherapy or behavioral therapy was not allowed during the study or within 3 months before screening.

Study Design

The screening period lasted 2 weeks. Patients were screened at an initial screening visit. A second visit followed the first screening week, during which the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version was again administered to confirm diagnosis. Patients were administered single-blind placebo during the second screening week.

After the placebo lead-in, patients were evaluated at a baseline visit to determine whether they continued to meet all entry criteria. Eligible patients were randomly assigned (1:1) to double-blind, flexible-dose treatment with either escitalopram or placebo. The escitalopram dose was fixed at 10 mg/day for the first 3 weeks of double-blind treatment; the escitalopram dose could be increased to 20 mg/day at the end of week 3 or 4. Dosage could subsequently be returned to 10 mg/day if limited by adverse events. Evaluations were scheduled at the end of 1, 2, 3, 4, 6, and 8 weeks of double-blind treatment.

Assessments

The CDRS-R was performed at the initial (screening) visit, baseline, and at the end of weeks 2, 4, 6, and 8 of double-blind treatment. The CDRS-R is a validated, semistructured, 17-item, clinician-rated instrument designed to measure severity of symptoms commonly associated with depression in children and adolescents; total scores range from 17 to 113, with higher numbers reflecting worsening of depression. The clinician's rating was based on a synthesis of separate interviews with the patient and the caregiver, using all available information to determine the most accurate rating of the symptom. The Clinical Global Impressions-Improvement (CGI-I) Scale[18] and CGI-S were administered at all postbaseline study visits; the CGI-S was also administered at baseline. These scales rate the severity of the patient's current state of mental illness (CGI-S) and the total improvement or worsening in the patient's mental illness relative to their baseline condition (CGI-I), based on the investigator's clinical opinion. For both scales, scores range from 1 to 7, with higher numbers reflecting worsening of illness. A CGI-I score of 1 or 2 ("very much improved" or "much improved") is generally used to define response. The Children's Global Assessment Scale (CGAS)[19] was administered at baseline and at the end of weeks 4 and 8 of the double-blind phase; CGAS was also administered on early termination. The CGAS is a clinician-rated scale that measures the overall functioning of children and adolescents. Scores range from 1 to 100, with "1 to 10" indicating "needs constant supervision" and "91 to 100" indicating "superior functioning."

Adverse events were either spontaneously reported by the patient or the patient's guardian or noted by the investigator. Relation to study medication was assessed for all adverse events by the investigator at the time the event was reported. Investigators also assessed whether an adverse event was "suggestive of self-harm." All adverse events considered by the investigator to be suggestive of self-harm were then further categorized as suicide attempt, suicidal ideation, self-injurious behavior (nonsuicidal), accidental overdose, or other. A *serious adverse event* (*SAE*) was defined as any event that was fatal or life threatening or led to hospitalization or prolongation of existing hospitalization or was associated with significant disability or incapacity, a congenital anomaly, or birth defect.

In addition to spontaneous reports, suicidality was assessed using patient self-report and clinician-rated instruments. The Suicidal Ideation Questionnaire–Junior High School Version (SIQ-JR),[20] a patient-rated questionnaire that identifies thoughts and cognitions about taking one's life, was administered at the initial (screening) visit, baseline, and at the end of weeks 1, 4, and 8 postbaseline. The SIQ-JR consists of 15 items rated on a 7-point scale, with higher numbers reflecting greater seriousness of suicidal ideation and cognition. The MC-SSRS, a clinician-rated instrument that rates suicidal ideation and the presence and type of suicidal behavior since the last visit (except at baseline, where the history of ideation and behavior was assessed), was administered at the initial (screening) visit, baseline, and all postbaseline visits. The two dimensions are classified on a six-point scale, with higher numbers reflecting greater seriousness of ideation and behavior; data from all sources, including the patient and guardian, are considered. The MC-SSRS is not yet validated. At the end of week 8, or on early termination, a physical examination and laboratory tests were performed, and ECG results were obtained.

Statistical Methods

Safety analyses were based on the safety population, which included all patients who received at least one dose of double-blind study medication. Efficacy analyses were performed on the intent-to-treat (ITT) population, which included all patients in the safety population who had at least 1 postbaseline CDRS-R assessment.

The primary prospectively defined efficacy measure was the change from baseline to week 8 in CDRS-R total score in the ITT population, using the last observation carried forward (LOCF) approach. The protocol-defined secondary assessment was CGI-I score at week 8; additional efficacy assessments were mean change from baseline in CGI-S and CGAS scores, CGI-I response rate (CGI-I score $\leq$2), CDRS-R response rate (at least 40% reduction in CDRS-R score from baseline), and remission (CDRS-R score $\leq$28).

Baseline imbalance between treatment groups in demographic and efficacy parameters was tested using a two-way analysis of variance model, with treatment group and study center as factors for continuous variables, and a Cochran-Mantel-Haenszel test controlling for study center for categorical variables. Treatment differences in the primary efficacy outcome were assessed using an analysis of

covariance (ANCOVA) model, with treatment group and study center as factors and baseline score as covariate. A similar ANCOVA model was used to assess treatment differences in CGAS and CGI-S scores. For CGI-I, the ANCOVA model for assessing treatment differences used baseline CGI-S score as covariate. Treatment differences in response and remission rates were assessed using a logistic regression model, with treatment group and baseline score as explanatory variables.

Assuming an effect size (treatment group difference relative to the pooled SD) of 0.325 on the primary efficacy variable, a sample size of 150 patients in each treatment group was estimated to provide at least 80% power to detect statistical treatment differences at a significance level of .05 using a two-sided test.

Descriptive statistics were generated for all safety results. For the SIQ-JR and the MC-SSRS, only the patients with a baseline assessment and at least one postbaseline assessment were included in the analyses. For the MC-SSRS, worsening from baseline was defined for the behavior scores as a change from zero at baseline to a score greater than zero, and for the ideation scores, a change from either zero (no ideation) or 1 (passive ideation) at baseline to a score greater than 1.

Reported results are LOCF unless otherwise specified. A mixed model for repeated-measures analysis was also conducted on the primary efficacy measure as a sensitivity analysis. In addition, the primary outcome (change in CDRS-R) was also assessed using the observed cases approach.

RESULTS

Of the 584 screened patients receiving at least 1 interview, 316 (54.1%) were randomly assigned to receive either placebo (n = 158) or escitalopram (n = 158). The safety population consisted of 157 placebo-treated and 155 escitalopram-treated patients. The ITT population consisted of 157 placebo- and 154 escitalopram-treated patients. A total of 133 (84.7%) placebo patients and 126 (81.3%) escitalopram patients completed 8 weeks of double-blind treatment. The most frequent reasons for discontinuation from the safety population were withdrawal of consent (5.7% placebo, 5.2% escitalopram) and loss to follow-up (3.8% placebo, 5.2% escitalopram). There were no significant differences between treatment groups for any reason for premature discontinuation (Fig. 1).

The mean (±SD) age of participants in the safety population was 14.5 ± 1.5 years in the placebo group and 14.7 ± 1.6 years in the escitalopram group (Table 1). The female subjects comprised 59% of both treatment groups. There were no statistically significant differences in the demographic characteristics of the treatment groups. In regard to baseline psychiatric characteristics, the mean (±SD) duration of the current depressive episode at study entry was 16.5 ± 15.4 months for the placebo group and 15.7 ± 17.4 months for the escitalopram group. The majority of patients in both groups were antidepressant naive (85.4% placebo, 81.3% escitalopram; p = 0.22), and less than 30% of the sample in either treatment group had recurrent

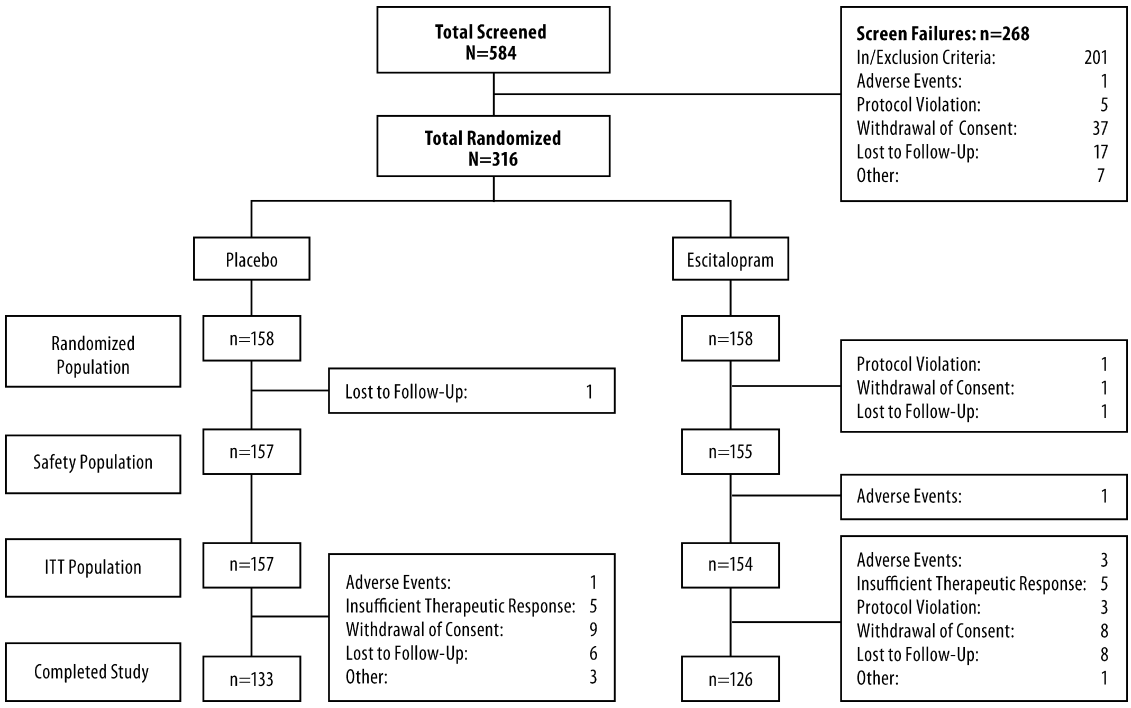

Fig. 1 Patient disposition.

TABLE 1
Baseline Characteristics, Safety Population

Demographic Characteristics	Placebo (n = 157)	Escitalopram (n = 155)
Age (mean ± SD), y	14.5 ± 1.5	14.7 ± 1.6
Sex (n, % female)	92 (58.6)	92 (59.4)
Race (n, % white)	123 (78.3)	113 (72.9)
Baseline psychiatric profile		
Duration of depressive episode (mean ± SD), mo	16.5 ± 15.4	15.7 ± 17.4
Age at onset (mean ± SD), y	12.3 ± 2.5	12.4 ± 2.6
Recurrent MDD (n, %)	44 (28.0)	46 (29.7)
Antidepressant naive (n, %)	134 (85.4)	126 (81.3)
Previous and/or ongoing secondary psychiatric disorder (n, %)	26 (16.6)	20 (12.9)

Note: MDD = major depressive disorder.

depression. Of the 52 patients who had received antidepressants previously, 16 of the 23 placebo patients and 16 of the 29 escitalopram patients had been considered nonresponders to treatment. The incidence of secondary psychiatric disorders (both previous and/or ongoing) was low (16.6% placebo, 12.9% escitalopram; p = .44), with the most common ones being attention-deficit/hyperactivity disorder (none of which were ongoing), enuresis, and generalized anxiety disorder.

Efficacy

There were significant differences between treatment groups in baseline CDRS-R and CGI-S scores, indicating greater depression severity in the escitalopram group; nevertheless, these differences were not clinically significant. In contrast, there was no difference in baseline CGAS scores (Table 2).

Primary Outcome. Escitalopram treatment produced significantly greater improvement in mean CDRS-R scores than placebo treatment at endpoint when analyzed using the LOCF approach (least squares mean difference [LSMD], −3.356; p = .022; Table 2), with an effect size of 0.27. Significant differences in CDRS-R scores favoring escitalopram over placebo were observed beginning at week 4 (LSMD, −3.371; p = .006; ANCOVA; Fig. 2). Sensitivity testing using the mixed model for repeated measures approach yielded similar findings at endpoint (LSMD, −3.129; p = .035). In the observed cases analysis, there was no difference in CDRS-R improvement between the escitalopram group (−24.6 ± 1.24) and the placebo group at week 8 (−21.9 ± 1.29; LSMD, −2.787; p = .071; ANCOVA).

Secondary and Other Outcomes. At endpoint, mean CGI-I scores were significantly better for the escitalopram group relative to the placebo group (LSMD,

TABLE 2
Efficacy Analyses at Week 8 (ITT Population; LOCF)

	Placebo		Escitalopram			
	N	LSM ± SEM	N	LSM ± SEM	LSMD (95% Confidence Interval)	p
Primary efficacy: CDRS-R total score						
CDRS-R baseline	157	56.0 ± 0.66	154	57.6 ± 0.66	—	.034
Change at week 8	157	−18.8 ± 1.27	154	−22.1 ± 1.22	−3.356 (−6.226 to −0.486)	.022
Secondary efficacy: CGI-I score						
LSM at week 8	157	2.6 ± 0.11	154	2.2 ± 0.11	−0.344 (−0.595 to −0.092)	.008
Additional efficacy						
CGI-S baseline	157	4.4 ± 0.04	154	4.6 ± 0.05	—	.007
CGI-S change at week 8	157	−1.4 ± 0.12	154	−1.8 ± 0.11	−0.37 (−0.64 to −0.10)	.007
CGAS baseline	157	51.9 ± 0.44	154	51.9 ± 0.51	—	.851
CGAS change at week 8	157	12.7 ± 1.15	154	14.9 ± 1.11	2.169 (−0.439 to 4.777)	.103
Response and remission rates (%, n)						
CGI-I response (≤2)	157	52.9 (83)	154	64.3 (99)		.03
CDRS-R response (40% decrease)	157	48.4 (76)	154	59.1 (91)		.06
Remission (CDRS-R ≤28)	157	35.7 (56)	154	41.6 (64)		.15

Note: Baseline treatment group imbalance was tested with a two-way ANOVA model; treatment differences were tested with an ANCOVA for continuous outcomes and a logistic regression model for categorical outcomes. ANCOVA = analysis of covariance; ANOVA = analysis of variance; CDRS-R = total score on the Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impressions-Severity; ITT = intent-to-treat; LOCF = last observation carried forward; LSM = least square mean; LSMD = least squares mean difference.

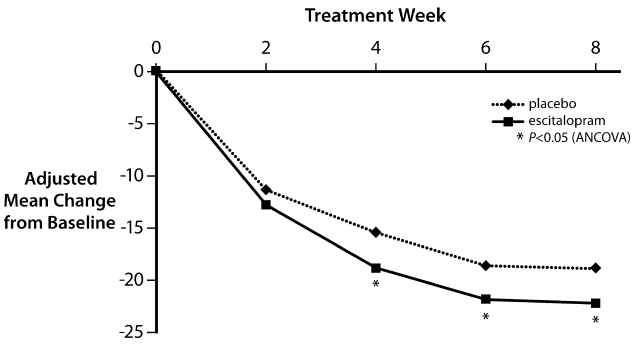

Fig. 2 Change in CDRS-R score by visit, ITT population (LOCF). CDRS-R = Children's Depression Rating Scale-Revised; ITT = intent-to-treat; LOCF = last observation carried forward.

−0.344; p = .008; ANCOVA). Results of additional efficacy parameters demonstrated that the mean change from CGI-S baseline to week 8 was significantly greater for escitalopram- than placebo-treated patients (LSMD, −0.37; p = .007; ANCOVA); no treatment difference in mean change from baseline to endpoint in CGAS scores was observed.

The percentage of CGI-I responders was significantly greater for escitalopram- than placebo-treated patients (LOCF; 64.3% versus 52.9%, respectively; p = .03; logistic regression); the difference was observed as early as week 3 and persisted through study endpoint. The number needed to treat was 8.75 (95% confidence interval 4.5–183). The largest drug-placebo difference was noted at week 4 (54.5% versus 36.3%; p = .001). However, when response was defined as a 40% or greater improvement from baseline in CDRS-R score, response rates at endpoint were 59.1% for escitalopram versus 48.4% for placebo (LOCF; p = .06; logistic regression). (A similar result was obtained when CDRS-R response rate was calculated as a 50% or greater improvement from baseline, after subtraction of the 17-point minimum CDRS-R score from the baseline score; in this case, the rates at endpoint were 62.0% for escitalopram versus 51.6% for placebo; LOCF; p = .07; logistic regression.) Remission rates (CDRS-R ≤28) at endpoint were 41.6% for escitalopram and 35.7% for placebo (LOCF; p = .15; logistic regression).

Tolerability

The mean (±SD) dose of escitalopram was 13.2 ± 2.9 mg/day; by tablet, the overall mean daily dose (±SD) of placebo was 1.4 ± 0.3 tablets per day and 1.3 ± 0.3 tablets per day of escitalopram. The majority of patients in both treatment groups had a dose increase (76.4% placebo, 68.4% escitalopram).

The rate of discontinuation because of adverse events did not differ for placebo (1 patient; 0.6%) versus escitalopram (4 patients; 2.6%; p = .21). Overall, adverse events were reported in 118 placebo patients (75.2%) and 121 escitalopram patients (78.1%). The adverse events reported with an incidence of 5% or higher in either group included headache, menstrual cramps, insomnia, nausea, abdominal pain, inflicted injury, pharyngitis, fatigue, influenza-like symptoms, rhinitis, vomiting, diarrhea, and upper respiratory tract infection (Table 3). Most of the adverse events coded with the preferred term *inflicted injury* were accidental injuries. The only adverse event that occurred in at least 5% of the escitalopram patients with an incidence of at least twice that in the placebo patients was influenza-like symptoms (3.2% placebo versus 7.1% escitalopram).

TABLE 3
Serious Adverse Events and Most Frequent (Incidence ≥5%) Adverse Events During Double-Blind Treatment, Safety Population

	Placebo (n = 157)	Escitalopram (n =155)
Serious adverse events		
Inflicted injury	0	n = 2[c]
Suicidal tendency	n = 1[a]	n = 1
Irritability	0	n = 1
Aggravated depression	n = 1	0
Most frequent adverse events, %		
Headache	25.5	25.2
Menstrual cramps[b]	15.2	10.9
Insomnia	6.4	10.3
Nausea	8.3	10.3
Abdominal pain	7.0	9.0
Inflicted injury	13.4	9.0
Pharyngitis	9.6	8.4
Fatigue	8.3	7.7
Influenza-like symptoms	3.2	7.1
Rhinitis	8.9	7.1
Vomiting	5.7	6.5
Diarrhea	3.2	5.2
Upper respiratory tract infection	7.6	5.2

[a] Occurred 10 days after discontinuation of double-blind placebo treatment (for insufficient therapeutic response) and initiation of commercially available escitalopram.

[b] Based on the number of female patients (92 placebo and 92 escitalopram).

[c] One patient who was sexually assaulted and one patient with self-injurious behavior.

In the safety population, two (1.3%) placebo and four (2.6%) escitalopram patients had an SAE (one of the placebo patients and all the four escitalopram patients were hospitalized for the SAEs). In the placebo group, 1 patient reported "suicidal tendency"; this report occurred 10 days after the discontinuation of double-blind placebo treatment (for insufficient therapeutic response) and initiation of commercially available escitalopram. The other SAE reported by a placebo-treated patient was aggravated depression. In the double-blind escitalopram-treated group, the four SAEs comprised one patient who was sexually assaulted, one patient with self-injurious behavior, one with suicidal ideation, and one with irritability.

Of all the adverse events reported during double-blind treatment, only 12 were considered by the investigator to be suggestive of self-harm. These included six (3.8%) placebo patients and six (3.9%) escitalopram patients. There was little overlap between these events and the SAEs—among SAEs, only the placebo patient with the suicidal tendency and the escitalopram patient with the self-injurious behavior received this classification. All six escitalopram events were further categorized by the investigator as non-suicidal self-injurious behavior.

The clinician-rated MC-SSRS was used to prospectively measure suicidality. Few participants had a worsening of suicidal behavior: 3 (2.3%) placebo and 2 (1.5%) escitalopram patients had an increase from baseline in MC-SSRS suicidal behavior scores, although 12 (9.4%) placebo and 12 (9.2%) escitalopram patients had an increase from baseline in MC-SSRS suicidal ideation scores.

At baseline, the SIQ-JR total score was similar between the two groups; the mean (±SD) scores were 15.2 ± 15.5 for the placebo group and 14.3 ± 14.4 for the escitalopram group. At endpoint, the mean (±SD) change from baseline in SIQ-JR scores was −4.6 ± 12.0 for placebo patients and −2.9 ± 10.2 for escitalopram patients ($p = .29$; t test).

Changes from baseline to endpoint in mean clinical laboratory values were similar for the two treatment groups, with the exception of decreased platelet count (-2.2×10^9/L placebo versus -7.6×10^9/L escitalopram). Mean vital sign changes from baseline to endpoint for the two groups were also small and similar for the two treatment groups. Mean weight gain was 1.2 lb for both treatment groups. There were no ECGs at endpoint that were considered abnormal and clinically significant by the investigator.

DISCUSSION

This large RCT demonstrates that escitalopram is effective for treating depression in adolescents and is consistent with the adolescent data available from the previous escitalopram trial.[14] The effect size compared with placebo (.27) is similar to the meta-analysis of all antidepressants in depressed youths, which had an effect size of 0.25,[6] and similar to the effect size for the adolescent group in two combined double-blind trials of fluoxetine (0.39).[21] It is also similar to the effect size of escitalopram in depressed adults (0.31).[22] Interestingly, the largest drug-placebo difference was at week 4. In fact, 85% (84/99) of the eventual escitalopram responders had responded by week 4, compared with 69% (57/83) of the placebo eventual responders.

The effectiveness of escitalopram was evident despite a robust placebo response in this trial (CGI-I placebo responder rate of 52.9%). In this study, there were 40 sites, which average to about 8 subjects per site, and previous studies with high numbers of sites and few subjects per site often led to higher placebo response rates.[23] Other factors contributing to the high placebo rate may include a large proportion of the subjects experiencing their first episode of depression and the limited comorbidity in the sample. The high placebo response was obtained despite the requirement for a high CDRS-R score at baseline (at least 45) and the use of a single-blind placebo lead-in period. Perhaps partly because of this high placebo response, the effect size we observed for escitalopram was modest.

For clinicians, a limitation of this trial is in determining the clinical significance of the results. Whereas the overall effect of medication is robust, the drug-placebo difference is modest. It is difficult to compare across studies to determine the relative efficacy of different antidepressants without an active comparator. For example, in the initial single-site fluoxetine study, the response rates were 56% for fluoxetine versus 33% for placebo based on CGI-I. The decrease in CDRS-R scores were −20.1 for fluoxetine and −10.5 for placebo, resulting in a fluoxetine/placebo difference of 23% for response rates and 9.6-point difference on CDRS-R total score. Such differences between active treatment and placebo are clinically relevant differences. As previously noted, the smaller

difference in this escitalopram study is primarily due to differences in placebo response between the two studies, so understanding placebo response in clinical trials is an important area for future studies.[23,24] In addition, placebo treatment in clinical trials, which includes both the placebo pill and extensive contact, does not occur in routine clinical care, and so understanding the relative effectiveness of escitalopram compared with no treatment or alternative nonmedication treatment is not answered by this trial.

Given the concerns regarding antidepressants and suicidality in depressed youth, we used three independent prospective methods to assess outcomes related to suicidality. The clinician-rated (MC-SSRS) and patient-rated (SIQ-JR) scales measured changes in suicidal ideation and (in the case of the MC-SSRS) behavior. Adverse event reports were also analyzed for their relation to self-harm (in the opinion of the investigator). It is important to note that suicidal ideation and behavior scores by the clinician and adolescent were independent from adverse events related to "self-harm." In other words, an adverse event report of suicidal ideation did not require that there be a corresponding shift in MC-SSRS ideation score and that a shift in MC-SSRS ideation or behavior did not necessarily "trigger" an adverse event report. They were simply two means of reporting data concerning suicidality. The fact that all adverse events suggestive of self-harm were judged by the investigator to be "nonsuicidal" illustrates the complexity of these events.

Suicidality events were observed at a similar incidence in both treatment groups, whether the results were obtained by spontaneous report or prospective clinician- or patient-rated scales. Based on spontaneous report, there were few suicidality events in this study; only six adverse events per group were considered to be suggestive of self-harm (and only 1 per group that was an SAE), consistent with the outcome of the clinician-rated MC-SSRS scale (which indicated only 5 behavioral events overall). Both clinician- and patient-rated scales yielded equivalent incidence of suicidal ideation in both groups. Because there were episodes of suicidal behavior, self-harm behavior, and worsening of suicidal ideation, regardless of treatment assignment, it stresses the need for treating clinicians to assess suicidal behaviors before and throughout treatment, particularly given that this sample was relatively free of suicidal behaviors at baseline.

The earlier escitalopram trial in depressed youths was of similar design to this study, except for the inclusion of children as well as adolescents; that study failed to show efficacy for the entire escitalopram treatment group relative to placebo.[14] Based on the study we report here, escitalopram seems to be a well-tolerated effective treatment for adolescents with MDD, which is consistent with the post hoc analysis of the adolescent subset from the earlier escitalopram trial.[14] At this time, little is known about long-term exposure to escitalopram in adolescents or the effect of escitalopram in adolescents with comorbid primary Axis I diagnoses, and these areas warrant further study.

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