Escitalopram in Adolescents With Generalized Anxiety Disorder: A Double-Blind, Randomized, Placebo-Controlled Study

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ABSTRACT

Background: Selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat pediatric anxiety disorders, including generalized anxiety disorder (GAD); however, their efficacy and tolerability are difficult to predict. This study evaluated the efficacy and tolerability of escitalopram in adolescents with GAD (*DSM-IV-TR*) and the impact of variants in *HTR2A* and serotonin transporter (*SLC6A4*) genes and cytochrome P450 2C19 (CYP2C19) phenotypes on response as well as CYP2C19 phenotype on escitalopram pharmacokinetics from February 2015 through November 2018.

Methods: Patients were treated with escitalopram (forced titration to 15 mg/d, then flexible titration to 20 mg/d) (n = 26, mean ± SD age: 14.8 ± 1.7 years) or placebo (n = 25, mean ± SD age: 14.9 ± 1.6 years) for 8 weeks. Outcomes were the change in scores on the Pediatric Anxiety Rating Scale (PARS) and Clinical Global Impressions (CGI) scales as well as vital signs and adverse events. Plasma escitalopram and desmethylcitalopram area under the curve during 24 hours (AUC_{0-24}) and maximum concentration (C_{max}) were determined and compared across CYP2C19 phenotypes.

Results: Escitalopram was superior to placebo for mean ± SD baseline-to-endpoint change in PARS (−8.65 ± 1.3 vs −3.52 ± 1.1, $P = .005$) and CGI scores, and increasing CYP2C19 metabolism was associated with decreases in escitalopram C_{max} ($P = .07$) and AUC_{0-24} ($P < .05$). Vital signs, corrected QT interval, and adverse events were similar in patients who received escitalopram and placebo.

Conclusions: Escitalopram reduces anxiety symptoms, and pharmacogenetics variables influence the trajectory and magnitude of improvement. Variation in CYP2C19 metabolism accounts for significant differences in escitalopram pharmacokinetics, raising the possibility that CYP2C19 phenotype should be considered when prescribing escitalopram.

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Characterized by uncontrollable, diffuse anxiety and accompanied by functionally impairing somatic and cognitive symptoms, generalized anxiety disorder (GAD) is among the most common anxiety disorders in adolescents.[1] Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and cognitive-behavioral therapy (CBT) reduce anxiety and improve functioning in many pediatric patients with GAD and related anxiety disorders.[2–5] However, 40% of youth either do not respond to these treatments[2] or experience treatment-limiting side effects.[6,7] Thus, there is an urgent need to develop and test additional interventions, to expand the treatment armamentarium, and to identify which patients will respond to these treatments.

While SSRIs represent the first-line pharmacotherapy for anxious youth, including those with GAD,[2,8] predicting treatment response is difficult. SSRI-related improvement varies considerably from patient to patient, often resulting in a trial-and-error process of medication selection and dosing. An additional shortcoming of SSRI treatment in pediatric anxiety disorders is the limited availability of data to aid clinicians in determining which patients will respond. In the Child/Adolescent Anxiety Multimodal Study (CAMS),[2] which compared sertraline, sertraline + CBT, CBT, and placebo, youth with severe anxiety required both an SSRI and CBT[9] while youth with less anxiety at baseline and those who did not have social anxiety disorder were more likely to experience remission with all treatments.[10] Despite studies of clinical and demographic factors that predict SSRI or SSRI + CBT response in anxious youth, examinations of biological (including pharmacogenetic) factors and SSRI response are rare in youth and virtually nonexistent in pediatric anxiety disorders.[11]

Cytochrome P450 2C19 (CYP2C19) metabolizes multiple SSRIs,[12,13] including citalopram and its *S*-enantiomer, escitalopram.[14] More than two dozen variants in the *CYP2C19* gene produce substantial variation in metabolic activity and include loss-of-function alleles (eg, no-function alleles **2–*9*) as well as alleles with increased activity (eg, **17*). In adults with reduced CYP2C19 metabolism, plasma escitalopram concentrations are higher than those in patients with normal CYP2C19 metabolism,[15] while patients with

Clinical Points

- Escitalopram reduces anxiety in adolescents with generalized anxiety disorder and is well tolerated.
- The *CYP2C19* genotype influences the trajectory and magnitude of improvement as well as escitalopram pharmacokinetics in anxious adolescents.

faster CYP2C19 metabolism have lower plasma escitalopram concentrations. The influence of CYP2C19 metabolizer status on escitalopram pharmacokinetics is well described in adults.[15] By contrast, only one small study (N = 9)[16] has examined this relationship in citalopram-treated youth and found "substantial correlation between CYP2C19 activity and *S*-citalopram concentration."(p809)

With these considerations in mind, we examined the efficacy and tolerability of escitalopram in adolescents with GAD as well as predictors of escitalopram-related improvement. On the basis of prior SSRI trials in youth and meta-analyses,[17] we hypothesized that escitalopram would be superior to placebo in decreasing anxiety. Finally, on the basis of studies in adults,[14] we hypothesized that faster CYP2C19 metabolism would be associated with decreased maximum concentration (C_{max}), exposure (area under the curve during 24 hours [AUC_{0-24}]), and ratios of escitalopram to its major metabolite, desmethylcitalopram.

METHODS

This Institutional Review Board–approved study (ClinicalTrials.gov identifier: NCT02818751) was conducted in accordance with Good Clinical Practice guidelines at a single academic site in the United States from February 2015 (first patient visit) through November 2018 (last patient visit). Written, informed consent and assent were obtained from all legal guardians and patients, respectively, prior to completion of any research procedures.

Participants

Outpatients aged 12–17 years who met *DSM-IV-TR* criteria for GAD were assessed using the Anxiety Disorders Interview Schedule (ADIS)[18]; those who had a Pediatric Anxiety Rating Scale (PARS) score ≥ 15 at screening and baseline and had a Clinical Global Impressions–Severity of Illness (CGI-S) score ≥ 4 were eligible. Patients were required to be medically stable and provide a negative urine drug screen and a negative urine pregnancy test (for girls) at screening. Patients with secondary diagnoses of separation or social anxiety disorder or panic disorder and/or agoraphobia were enrolled, provided that GAD was the primary diagnosis; however, patients with current major depressive disorder (MDD) or any history of *DSM-IV-TR* bipolar disorder, psychotic disorder, obsessive-compulsive disorder, or posttraumatic stress disorder were excluded. Stable concomitant psychotherapy was allowed during the study. Use of antidepressants, antipsychotics, anticonvulsants, stimulants, or benzodiazepines was prohibited, although caffeine, nonopiate analgesics, nonsedating H_1 and H_2 antagonists, and oral contraceptives were allowed.

Study Treatment

Randomization to escitalopram or placebo (1:1) was assigned, in blocks of 4, by investigational pharmacists and was stratified by sex using a random number generator. Patients, caregivers, and investigational staff were blind to treatment assignment. Escitalopram was initiated at 5 mg daily for 2 days and titrated to 10 mg daily for 7 days and then 15 mg daily. At the week 4 and 6 visits, escitalopram could be titrated to 20 mg daily. The study incorporated a 1-week screening period and an 8-week double-blind treatment period.

Assessments

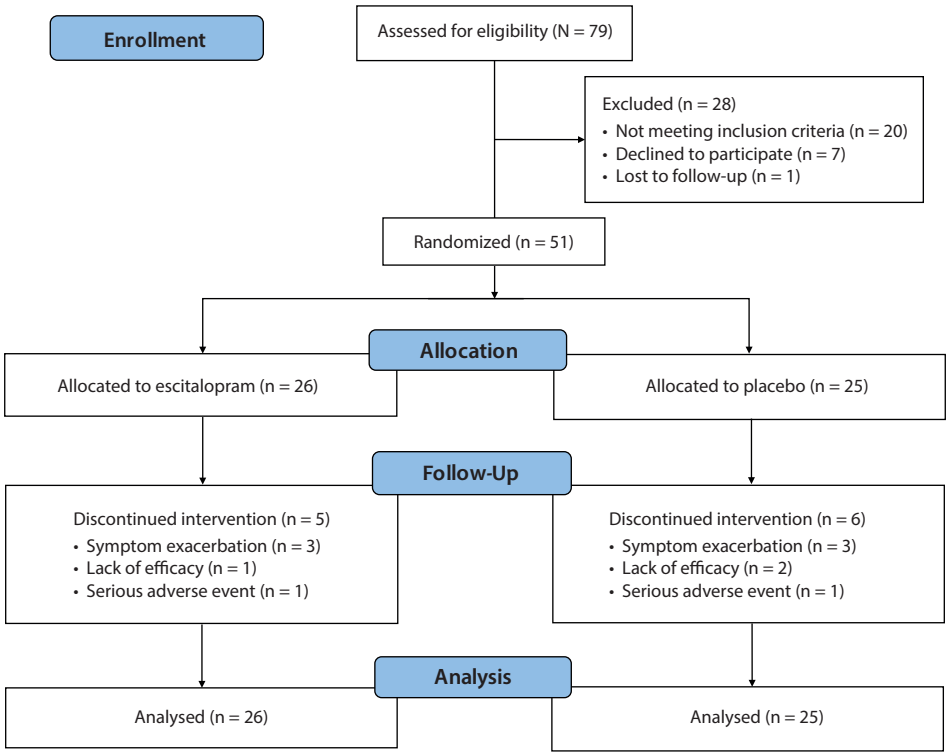
The primary efficacy outcome was change in PARS score from baseline to week 8 and change from baseline in CGI-S and CGI-Improvement scale (CGI-I) response (defined as a CGI-I score of 1 or 2). All efficacy assessments were administered at weeks 1, 2, 4, 6, and 8 and/or at early termination and were completed in an outpatient setting. Efficacy measures were administered by a blinded study physician who underwent training on the use of the instrument and met predetermined interrater reliability criteria as previously described.[17] Because of the relatively small sample and the single-site setting, the same rater evaluated each patient during the course of the trial.

Spontaneously reported adverse events (AEs), pulse, blood pressure, and weight were recorded at every visit. Electrocardiograms (ECGs) were collected at baseline and weeks 2 and 8 or early termination. The Columbia–Suicide Severity Rating Scale (C-SSRS) was completed at all visits, and the Children's Depression Rating Scale–Revised (CDRS-R)[19] was used to evaluate concurrent depressive symptoms at each visit. AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA, v. 22.0, www.medra.org) system organ class and high level group terms, and activation-cluster symptoms were categorized as previously described[20,21] and included activation, worsening insomnia, irritability, impulsivity, and worsening anxiety. A physical examination was performed at screening and week 8. The Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II),[22] was used to estimate IQ at screening.

Pharmacogenetic Testing

Genomic DNA was collected with a buccal swab using a commercially available pharmacogenomic test (Myriad Genetics; Mason, Ohio). Genotyping assessed 9 allelic variations in *CYP2C19*. Clinical Pharmacogenetics Implementation Consortium guidelines[23] were used to assign a CYP2C19 metabolizer phenotype from the alleles present for each patient. Poor metabolizers have 2 no-function alleles; intermediate metabolizers have 1 no-function and 1 normal or increased function allele (eg, **1/*2*, **2/*17*); normal metabolizers have 2 normal function alleles (**1/*1*);

Figure 1. Study Flow[a]



[a]During the study, all patients and study staff remained unaware of trial group assignments. Of 134 referrals, 79 were enrolled and 51 were randomized.

rapid metabolizers have 1 increased function allele and 1 normal function allele (**1/*17*); and ultrarapid metabolizers have 2 increased function alleles (**17/*17*).[23] *HTR2A* and *SLC6A4* were genotyped as previously described.[24]

Escitalopram and Desmethylcitalopram Plasma Measures

Escitalopram and desmethylcitalopram concentrations were determined using high-performance liquid chromatography at endpoint (or early termination), as previously described.[25] Then, based on the escitalopram dose, sampling time, and compliance for each patient, plasma escitalopram concentrations were modeled using MwPharm (version 3.82; MediWare BV; Groningen, the Netherlands), which permitted allometric scaling and incorporated each patient's weight, height, and age at the time of pharmacokinetic sampling, as previously described.[26] From these models, AUC_{0-24} and C_{max} for each adolescent for which pharmacokinetic samples were available were determined and compared across CYP2C19 phenotypes at a modeled oral escitalopram dose of 15 mg/d (the forced-titration dose in this study). Adherence was assessed by pill count at each visit.

Statistical Methods

Sample size consisted of 32 patients in the escitalopram group and 32 patients in the placebo group, and 80% power was used to detect group differences of ≥0.7 (Cohen *d*). All analyses of continuous measures included randomized patients with both a baseline and at least 1 post-baseline value for the variable being analyzed. Imputation occurred via last observation carried forward (LOCF). For categorical outcomes (eg, adverse events), treatments were compared with the use of the Pearson χ^2 or posterior probabilities and logistic regression, as appropriate. For continuous outcomes, logarithmic mixed-effects models were employed to determine predicted mean outcome values at weeks 0, 1, 2, 4, 6, and 8 (or early termination) to examine group differences. Mixed-effects models included indicator variables for week and treatment as fixed effects. Each model was created with a limited number of covariates (eg, age, sex) and refined as previously described to obtain the most parsimonious response model.[27,28] Changes from baseline in CGI-S and CGI-I scores were examined using the same approach.

For pharmacogenomic predictors of treatment response, Bayesian logistic regression models of categorical response (CGI-I score ≤2) were utilized to evaluate the impact of the predictors. Average treatment response rate was assumed to be uniformly distributed between 0 and 1 for all analyses. For change in symptom severity, a logarithmic trajectory model was utilized. All model parameters for average change in symptoms were modeled with an uninformative normal prior, ie, normally distributed with a mean of

Table 1. Demographic and Clinical Characteristics of Study Patients[a]

Baseline Characteristic	Escitalopram (n = 26)	Placebo (n = 25)
Age, mean ± SD, y	14.8 ± 1.7	14.9 ± 1.6
Female	20 (77)	19 (76)
Duke Tanner Stage, female/male		
Stage 3	6 (23)/3 (12)	1 (4)/0 (0)
Stage 4	5 (19)/3 (12)	10 (40)/5 (20)
Stage 5	9 (35)/0 (0)	8 (32)/1 (4)
Race		
Asian	0 (0)	2 (8)
Black and African American	1 (4)	1 (4)
White	23 (88)	20 (80)
Other	2 (8)	2 (8)
Hispanic or Latino	3 (12)	0 (0)
Full scale IQ, mean ± SD	106 ± 12	105 ± 10
PARS score, mean ± SD	18 ± 2	17 ± 2
CGI-S score, median	4	4
CDRS-R score, mean ± SD	33 ± 4	32 ± 6
PSC score, mean ± SD	23.12 ± 3.15	30.76 ± 4.99
Co-occurring disorders		
Separation anxiety	4 (15)	5 (20)
Panic disorder	13 (50)	15 (60)
Agoraphobia	7 (27)	7 (28)
ADHD	5 (19)	4 (16)
Specific phobia	9 (35)	3 (12)
Prior SSRI/SNRI treatment	6 (23)	7 (28)
Current psychotherapy treatment	3 (12)	5 (20)
CYP2C19 genotype		
**2/*2*	1 (4)	
**1/*2*	5 (19)	
**1/*1*	10 (38)	
**1/*17*	4 (15)	
**2/*17*	3 (12)	
**4/*17*	2 (8)	
**17/*17*	1 (4)	

[a]Values are shown as n (%) unless otherwise noted.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CDRS-R = Children's Depression Rating Scale–Revised, CGI-I = Clinical Global Impressions–Improvement scale, CGI-S = Clinical Global Impressions–Severity of Illness scale, PARS = Pediatric Anxiety Rating Scale, PSC = Physical Symptom Checklist, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

zero and large variance, $N(\mu = 0, \sigma^2 = 1{,}000)$. Predictors included the CYP2C19 phenotype (intermediate vs normal metabolizer), a logarithmic trend, and age and sex. Model sets were refined, as previously described,[28] based on the parametric fit in addition to *P* values and the Bayesian and Akaike Information Criteria (BIC and AIC, respectively). Models were evaluated for omitted variables bias and for the inclusion of irrelevant variables. Then, for any statistically significant predictors of treatment response, models of the log trajectory response probability were developed. *SLC6A4* genotypes were grouped into high (eg, L/L and L/S) and low (eg, S/S) expression levels for analysis and having a G/G genotype (vs A/G or A/A) for the rs6311 (−1438 G > A) single nucleotide polymorphism in the *HTR2A* gene.

The relationship between CYP2C19 phenotype and escitalopram AUC_{0-24} and C_{max} at 15 mg/d as well as the relationship between CYP2C19 phenotype and desmethylcitalopram:escitalopram ratios were examined using analysis of variance (ANOVA) tests. Post hoc explorations of medication exposure and clinical outcomes were limited to response and the presence of activation-cluster symptoms given that fluoxetine[29] and fluvoxamine[20] concentrations and exposure have been associated with activation in pediatric anxiety disorders. C_{max} and AUC_{0-24} were compared between patients with and without activation and between responders and nonresponders (at week 8/early termination) with Student *t* tests and examined in the aforementioned multivariate logistic regression. All analyses were performed with R (version 3.3.1; 2020; R Foundation for Statistical Computing) and Julia (version 1.2.0),[30] and findings were considered statistically significant at the 5% threshold.

RESULTS

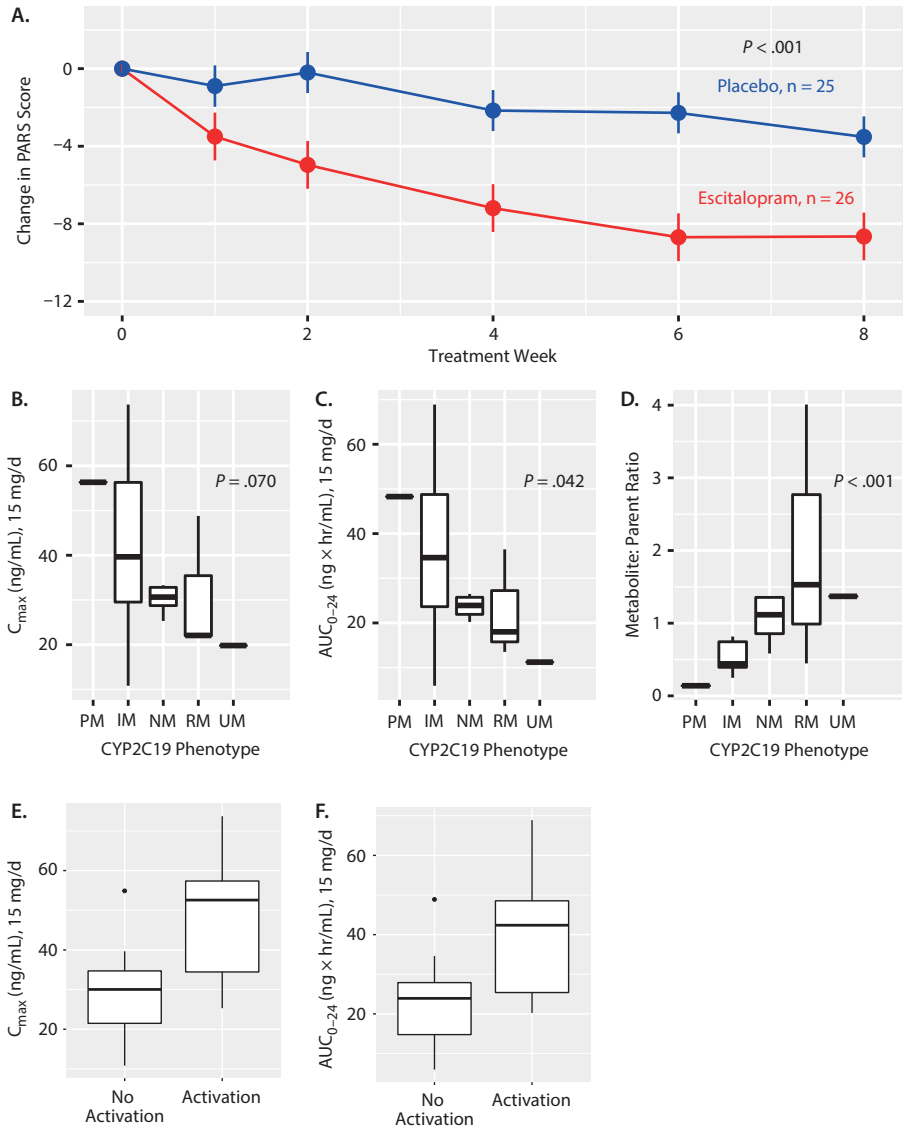
Patients

Patients were recruited between 2015 and 2018, and the last follow-up visit was completed in 2019. Figure 1 illustrates patient flow during the study. Baseline characteristics did not significantly differ between treatment groups (Table 1). Of 79 individuals screened, 51 were randomly assigned to treatment, took at least 1 dose of escitalopram (or placebo), and were included in the analyses (escitalopram n = 26; placebo, n = 25). The majority of patients in both groups were girls (placebo: n = 20, 77%; escitalopram n = 19, 76%) and white (placebo: n = 23, 88%; escitalopram n = 20, 80%). Mean ± SD baseline PARS scores were 18 ± 2 and 17 ± 2 for patients randomized to escitalopram and placebo, respectively, and reflect moderate-to-severe anxiety. Mean ± SD CDRS-R scores were similar between groups (escitalopram: 33 ± 4; placebo: 32 ± 6), although these scores largely reflect overlapping anxiety and depressive symptoms rather than symptoms of MDD per se (Table 1). Finally, approximately three-quarters of the sample was SSRI/SNRI-naive (Table 1). The most common reasons for discontinuation were lack of efficacy or persistent or worsening anxiety, and these rates did not differ between groups (escitalopram: n = 3 [12%]; placebo: n = 5 [20%], *P* = .429). Nine percent of efficacy measures were imputed by LOCF, and the frequency of missing data did not differ between patients receiving escitalopram and those who received placebo (*P* = .619)

Efficacy

The trajectory of improvement over the 8-week trial and improvement at week 8 was significantly greater in escitalopram-treated patients compared to those receiving placebo (both *P* values < .001, Figure 2A). At week 8 (LOCF), the mean ± SD change in PARS score in escitalopram-treated patients was −8.65 ± 1.31 compared to −3.52 ± 1.06 in patients receiving placebo (95% CI, −8.57 to −1.70; *P* = .005). The trajectory of improvement in anxiety (escitalopram vs placebo) over time—as measured by the PARS—was not associated with age (*P* = .478), age-by-time (*P* = .155), sex (*P* = .870), or sex-by-time (*P* = .708) but was associated with baseline PARS score (*P* < .001). In the logistic response trajectory model, CGI-I response (ie, CGI-I score ≤ 2) was greater in escitalopram-treated patients compared

Figure 2. (A) Change Over Time in PARS Score for Escitalopram Versus Placebo[a]; Impact of CYP2C19 Phenotype on (B) Maximum Concentration (C_{max}), (C) Area Under the Curve During 24 Hours ($AUC_{0–24}$), and (D) Metabolite:Parent Drug Ratio[b]; and Difference in (E) C_{max} and (F) AUC Between Patients With and Without Activation Symptoms[c]



[a]Values shown as mean ± SE.
[b]Boxplots for parts B, C, and D show median (IQR) and minimum and maximum values.
[c]Boxplots for parts E and F show median (IQR) and minimum and maximum values and outliers.
Abbreviations: CYP2C19 = cytochrome P450 2C19, IM = intermediate metabolizer, IQR = interquartile range, NM = normal metabolizer, PM = poor metabolizer, RM = rapid metabolizer, UR = ultrarapid metabolizer.

to those receiving placebo ($P < .001$) and was associated with age ($P = .041$), with younger patients experiencing greater improvement. At week 8 (LOCF), 16 (62%) of 26 escitalopram-treated patients compared to 6 (24%) of 25 who received placebo had a CGI-I score ≤ 2 (95% CI, 0.95 to 0.578; $P = .0039$). Finally, the number needed to treat (NNT) for escitalopram was 3.

Mean improvement in CGI-S score (treated as a continuous variable) was statistically significantly greater for escitalopram-treated patients compared to those receiving placebo ($P < .001$). At week 8 (LOCF), the mean ± SD CGI-S score in escitalopram-treated patients was 2.8 ± 0.3 compared to 3.6 ± 0.2 in patients receiving placebo ($P = .032$).

Adverse Events and Discontinuation

Rates and reasons for early discontinuation are shown in Figure 1 and did not significantly differ between escitalopram and placebo groups (escitalopram, n = 5 [19%]; placebo, n = 6 [24%]). One escitalopram-treated patient and 1 patient who received placebo each experienced a serious adverse event (placebo, hospitalization for verbal aggression and increased irritability; escitalopram, aborted suicide attempt).

Table 2. Spontaneously Reported Treatment-Emergent Adverse Events

System Organ Class (MedDRA) and Adverse Event	Escitalopram (n = 26), n (%)	Placebo (n = 25), n (%)
Ear and labyrinth		
Otitis media	0 (0)	1 (4)
Gastrointestinal		
Abdominal pain	10 (38)	9 (36)
Constipation	0	0
Diarrhea or loose bowel movements	0	5 (20)
Dry mouth	0	2 (8)
Gastroenteritis	2 (8)	2 (8)
Gastroesophageal reflux	1 (4)	0
Nausea	8 (31)	11 (44)
Vomiting	2 (8)	3 (12)
General		
Appetite, decreased	4 (15)	4 (16)
Appetite, increased	2 (8)	1 (4)
Chills	0	0
Fever	1 (4)	2 (8)
Flushing	0	0
Hyperhidrosis	1 (4)	2 (8)
Somnolence or fatigue	9 (35)	5 (20)
Investigations		
Weight gain	1 (4)	0
Weight loss	1 (4)	1 (4)
Musculoskeletal and connective tissue		
Arthralgias	1 (4)	2 (8)
Leg cramping	0	2 (8)
Myalgias	1 (4)	0
Nervous system		
Blurred vision	0	0
Dizziness	2 (8)	0
Headache	15 (58)	12 (48)
Syncope	0	1 (4)
Vivid or unusual dreams	5 (19)	3 (12)
Psychiatric		
Activation-cluster symptoms	7 (27)	5 (20)
Insomnia	5 (19)	5 (20)
Reproductive system and breast		
Dysmenorrhea	4 (15)	2 (8)
Respiratory, thoracic, and mediastinal		
Epistaxis	1 (4)	0
Nasal congestion	5 (19)	2 (8)
Sinusitis	1 (4)	0
Respiratory tract infection, pharyngitis	10 (38)	5 (20)
Yawning	0	0
Skin and subcutaneous tissue		
Acne	1 (4)	0
Dry skin	0	1 (4)
Hair loss	0	1 (4)
Rash	1 (4)	0
Vascular		
Bruising	4 (15)	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

Compared to baseline, there were 6 events of C-SSRS–defined worsening in patients receiving escitalopram compared to 2 events in patients receiving placebo; 1 escitalopram-treated patient experienced an aborted suicide attempt. Two patients receiving escitalopram, compared to 1 patient receiving placebo, engaged in self-injurious behavior (superficial cutting, without penetration of subcutaneous tissue). The emergence or worsening of suicidality did not significantly differ between escitalopram-treated patients and those receiving placebo ($P = .449$).

Spontaneously reported AEs are shown in Table 2 and did not differ between groups, with the exception of bruising, which trended toward being more common in escitalopram-treated patients compared to those receiving placebo (4 vs 0 patients, $P = .056$). Finally, in the post hoc exploration of activation and medication exposure, activation was associated with greater escitalopram C_{max} ($P = .04$) and AUC_{0-24} ($P = .04$) in patients for whom pharmacokinetic sampling was completed (n = 18).

Vital Signs and Electrocardiographic Data

Escitalopram-treated patients did not significantly differ from those receiving placebo with regard to mean ± SD baseline-to-endpoint changes in pulse (escitalopram: 1.54 ± 2.13 bpm, placebo: 1.59 ± 2.92 bpm; $P = .99$), systolic blood pressure (escitalopram: −1.20 ± 2.09 mm Hg, placebo: 0.66 ± 2.74 mm Hg; $P = .583$), diastolic blood pressure (escitalopram: −0.066 ± 1.73 mm Hg, placebo: −3.26 ± 2.21 mm Hg; $P = .251$). Similarly, no differences in change in weight were observed between groups (escitalopram: −0.47 ± 0.35 kg, placebo: −0.67 ± 0.44 kg; $P = .716$). No patients in either group had prolonged corrected QT interval (QTc) > 500 msec at any time during the study, and QTc changes were not significantly different between escitalopram (−6.63 ± 5.05) and placebo (0.99 ± 4.13) ($P = .238$).

Predictors of Treatment Response to Escitalopram

For the change in PARS score in escitalopram-treated patients, greater improvement over time was associated with being an intermediate CYP2C19 metabolizer ($P < .016$).

For response (CGI-I score ≤ 2) over time, a logistic regression including age, sex, time, CYP2C19 phenotype (normal or intermediate), *HTR2A* (G/G vs G/A or A/A), and *SLC6A4* (S/S vs S/L or L/L) found that greater response was significantly associated with having at least one long allele of *SLC6A4* ($P = .005$), being an intermediate CYP2C19 metabolizer ($P = .015$), and having a G/G diplotype for the *HTR2A* rs6311 allele ($P = .037$).

Plasma escitalopram and desmethylcitalopram concentrations were determined in 18 youth (nearly 70% of escitalopram-treated patients), including poor (n = 1), intermediate (n = 7), normal (n = 6), rapid (n = 3), and ultrarapid (n = 1) metabolizers. Escitalopram AUC_{0-24} significantly decreased with increased CYP2C19 metabolism at 15 mg/d (ANOVA test for linear trend, $P = .042$; Figure 2B). C_{max} trended toward being higher in slower metabolizers, relative to faster metabolizers, at 15 mg/d (ANOVA test for trend, $P = .070$; Figure 2C). Desmethylcitalopram:escitalopram ratios were increased in patients with faster CYP2C19 metabolism relative to those with slower metabolism ($P < .001$, Figure 2D).

Escitalopram exposure (mean ± SD AUC_{0-24}) at the 15-mg/d dose did not differ between week 8 (or early termination) responders (n = 11, 26.98 ± 10.8) and nonresponders (n = 7, 32.45 ± 20.1, $P = .490$). Similarly, desmethylcitalopram:escitalopram: ratios did not differ between responders 1.07 ± 0.727 and nonresponders

(1.15 ± 1.319, P = .876). In the post hoc logistic regression of pharmacokinetic parameters (ie, C_{max}, AUC_{0-24}), age, CYP2C19 phenotype, and response (CGI-I score ≤ 2), higher C_{max} and AUC_{0-24} were not statistically significantly associated with response (P = .067 and P = .062, respectively). Models incorporating desmethylcitalopram:escitalopram ratios did not suggest an association with response (P = .342). Finally, patients who experienced activation symptoms had higher C_{max} (P = .040) and AUC_{0-24} (P = .040) compared to those who did not (Figures 2E and 2F).

DISCUSSION

To our knowledge, this double-blind, placebo-controlled trial of escitalopram is the first in pediatric patients with GAD. Our findings demonstrate the superiority of escitalopram relative to placebo in both magnitude and trajectory of improvement. This study suggests the potential predictive utility of pharmacogenetic markers of treatment response and, for the first time in anxious youth, links escitalopram pharmacokinetics with CYP2C19 metabolizer status and side effects.

Consistent with most studies of SSRIs in pediatric anxiety disorders,[2,3] escitalopram was superior to placebo in reducing anxiety symptoms. In fact, the NNT in this study is similar to that in other studies of SSRIs in pediatric anxiety disorders,[2] and placebo response was relatively low (24%), which is similar to findings of most trials of SSRIs in pediatric anxiety disorders.[2,3] Similar to other studies of SSRIs in pediatric anxiety disorders, escitalopram was well-tolerated.[31] The side effects observed herein were consistent with larger trials, although the sample size and duration of the trial decreased our ability to explore longer-term side effects (eg, weight gain), which has been reported in pediatric patients with depressive and anxiety disorders, particularly those who are slower CYP2C19 metabolizers.[32] Additionally, with regard to acute side effects, we observed a relationship between activation-related symptoms and both C_{max} and AUC_{0-24} in the pharmacokinetic cohort, which is consistent with two other reports of SSRI exposure-related activation.[20,29] Thus, in anxious youth, activation has been demonstrated to be associated with higher exposure to fluoxetine, fluvoxamine, and now escitalopram, although it has not been associated with dose in any of these studies. These findings remind clinicians to consider medication exposure rather than just dose in assessing SSRI-related side effects.

The findings that (1) CYP2C19 phenotype predicts escitalopram exposure as well as response trajectory (and magnitude) and, (2) in our post hoc analyses, escitalopram levels are associated with response (at a 6% significance threshold) and activation suggest that we might reconsider the role of therapeutic drug monitoring in psychiatry. Guidelines suggest "target doses" for SSRIs that are often based on large randomized controlled trials in pediatric patients. However, a "target dose" fails to acknowledge variability in the actual exposure to the medication that may be dependent on individual differences in metabolism. Additionally, the exposure-response relationship suggested herein is very likely confounded by AEs. Patients with higher levels may be more likely to respond, but may also be more likely to discontinue medication.

While this double-blind placebo-controlled study of escitalopram is the first in pediatric anxiety disorders and the first pediatric study to prospectively examine the impact of pharmacodynamic and pharmacokinetic genes on treatment response, as well as the relationship between metabolizer status and medication exposure, several important limitations warrant additional discussion. First, the sample was small, racially homogeneous (> 80% white), relatively treatment naive (~75% without prior SSRI/SNRI treatment), and primarily female and was recruited from a single site. While this homogeneity potentially reduced outcome variability, it limited our ability to examine some predictors of differential outcomes. The racial homogeneity also obscured our ability to examine differences in *CYP2C19* alleles. The "hypermetabolic" **17* allele is twice as common in African American (19%) and US white individuals (18%) compared to Hispanic individuals, which could account for differences in tolerability or efficacy across demographics.[33] Second, the forced-flexible escitalopram titration that potentially increased response decreased treatment dose variability (ie, patients received either 15 mg/d or 20 mg/d). Our ability to examine dose was limited; however, it is noteworthy that there was substantial variability in medication exposure (ie, AUC_{0-24}). Third, while we examined escitalopram exposure and response, tolerability (which may also relate to response) confounds these models, and there is endogeneity among variables. Fourth, we included patients with severe anxiety and significant comorbidity (eg, more than half of the sample had panic disorder and nearly one-third had agoraphobia) which may have amplified the medication-placebo difference and may limit generalizability. Prior studies suggest that less severe pathology is associated with a greater placebo response.[34] Fourth, patients were not systematically followed after completion of this acute treatment trial. Fifth, we have focused on a single developmental period (adolescence) and a singular diagnosis (GAD); however, anxiety disorders often emerge prior to adolescence.[35] Many[2,36,37] but not all[3,4] studies of pharmacotherapy in anxious youth focus on generalized, separation, and social anxiety disorders as they commonly co-occur, share risk factors, and respond similarly to psychotherapy and pharmacotherapy.[38] However, we believe that given the degree of overlap with other separation and social anxiety disorders and our use of a global measure of anxiety (PARS), our findings could be extrapolated to separation and social anxiety. Sixth, while we focused on adolescents to minimize pharmacokinetic confounds and to be consistent with the US Food and Drug Administration–labeled age range for escitalopram, this focus limits extrapolation of these findings to younger patients. Last, our small sample precluded analysis of other pharmacokinetic genes (eg, *CYP2D6* and *CYP3A4*), so only

the primary metabolizing enzyme (CYP2C19) was analyzed; the extreme phenotypes of *CYP2D6* and *CYP3A4* were too infrequent in this study sample.

This study has many implications for clinicians treating adolescents with GAD and provides preliminary answers to important questions: (1) Is escitalopram effective in treating you with anxiety? (2) How quickly will patients respond? and (3) Does CYP2C19 metabolism affect escitalopram pharmacokinetics in youth? Finally, the answers to these questions, although incomplete, provide a scaffold for larger studies of pharmacodynamic and pharmacokinetic predictors of treatment response and studies that leverage variability in exposure to inform medication dosing and selection.

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