

# Lack of Efficacy of Citalopram in Children With Autism Spectrum Disorders and High Levels of Repetitive Behavior

## *Citalopram Ineffective in Children With Autism*

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**Context:** Selective serotonin reuptake inhibitors are widely prescribed for children with autism spectrum disorders.

**Objectives:** To determine the efficacy and safety of citalopram hydrobromide therapy for repetitive behavior in children with autism spectrum disorders.

**Design:** National Institutes of Health–sponsored randomized controlled trial.

**Setting:** Six academic centers, including Mount Sinai School of Medicine, North Shore–Long Island Jewish Health System, University of North Carolina at Chapel Hill, University of California at Los Angeles, Yale University, and Dartmouth Medical School.

**Participants:** One hundred forty-nine volunteers 5 to 17 years old (mean [SD] age, 9.4 [3.1] years) were randomized to receive citalopram (n = 73) or placebo (n = 76). Participants had autistic spectrum disorders, Asperger disorder, or pervasive developmental disorder, not otherwise specified; had illness severity ratings of at least moderate on the Clinical Global Impressions, Severity of Illness Scale; and scored at least moderate on compulsive behaviors measured with the Children's Yale-Brown Obsessive Compulsive Scales modified for pervasive developmental disorders.

**Interventions:** Twelve weeks of citalopram hydrobromide (10 mg/5 mL) or placebo. The mean (SD) maximum dosage of citalopram hydrobromide was 16.5 (6.5) mg/d by mouth (maximum, 20 mg/d).

**Main Outcome Measures:** Positive response was defined by a score of much improved or very much improved on the Clinical Global Impressions, Improvement subscale. An important secondary outcome was the score on the Children's Yale-Brown Obsessive Compulsive Scales modified for pervasive developmental disorders. Adverse events were systematically elicited using the Safety Monitoring Uniform Report Form.

**Results:** There was no significant difference in the rate of positive response on the Clinical Global Impressions, Improvement subscale between the citalopram-treated group (32.9%) and the placebo group (34.2%) (relative risk, 0.96; 95% confidence interval, 0.61-1.51;  $P > .99$ ). There was no difference in score reduction on the Children's Yale-Brown Obsessive Compulsive Scales modified for pervasive developmental disorders from baseline (mean [SD], -2.0 [3.4] points for the citalopram-treated group and -1.9 [2.5] points for the placebo group;  $P = .81$ ). Citalopram use was significantly more likely to be associated with adverse events, particularly increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypy, diarrhea, insomnia, and dry skin or pruritus.

**Conclusion:** Results of this trial do not support the use of citalopram for the treatment of repetitive behavior in children and adolescents with autism spectrum disorders.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00086645

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Group Information: The STAART Psychopharmacology Network members are listed on page 589.

**P**ERVASIVE DEVELOPMENTAL DISORDERS (also called "autism spectrum disorders" [ASDs]), including autistic disorder, Asperger disorder, and pervasive developmental disorder, not otherwise specified, are neurodevelopmental disorders of early childhood onset characterized by impairments in social interaction, communication problems, unusual preoccupations, and repetitive behavior.<sup>1</sup> Collectively, the prevalence of ASDs is es-

timated at 6 cases per 1000.<sup>2</sup> Although no medications are approved by the Food and Drug Administration for core symptoms of ASDs, medication use in this population has become increasingly common.<sup>3</sup> The global

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market for autism therapeutics is estimated at \$2.2 to \$3.5 billion.<sup>4</sup> Selective serotonin reuptake inhibitors (SSRIs) account for the greatest global market share (59%),

reflecting the combination of cost and frequency of prescription.<sup>4</sup>

The type, frequency, and intensity of repetitive behavior in individual children with ASDs vary widely but often persist over time. In addition, repetitive behavior is the strongest predictor that an early ASD diagnosis will endure.<sup>5</sup> Repetitive behavior may involve stereotypic movements, inflexible routines, repetitive play, and perseverative speech, often interfering with many facets of life. Anxiety, protest, aggression, and self-injury may occur when these behaviors are interrupted. Because of suggested similarities between repetitive behavior in ASDs and obsessive-compulsive disorder<sup>6-8</sup> and the findings of serotonin system abnormalities in autism,<sup>9</sup> antiobsessional agents such as SSRIs have long been of interest.<sup>10</sup>

Preliminary experience with the serotonergic tricyclic antidepressant clomipramine hydrochloride showed moderate benefit for anger and ritualized behaviors compared with the noradrenergic desipramine hydrochloride.<sup>11</sup> However, a subsequent trial comparing clomipramine, the antipsychotic haloperidol, and placebo in adults with ASDs showed no differentiation between clomipramine use and placebo and a high rate of adverse events.<sup>12</sup> The SSRI fluvoxamine maleate was superior to placebo for repetitive behavior, aggression, and social relatedness in adults with autism.<sup>13</sup> However, in a placebo-controlled study<sup>14</sup> of the same medication in children, only 1 of 18 subjects demonstrated improvement on active drug; furthermore, adverse events, including hyperactivity, insomnia, agitation, and aggression, occurred in 14 of 18 children treated with fluvoxamine, suggesting unusual sensitivity of children with ASDs to this SSRI. A 2005 single-site placebo-controlled study<sup>8</sup> of the SSRI fluoxetine hydrochloride revealed that low dosages of medication were well tolerated and were associated with modest but significant benefit. Despite the relative dearth of evidence supporting their use, SSRIs are among the most frequently used medications for children with autism,<sup>3,15</sup> partially because of their perceived safety. Controlled clinical trials are needed to inform this practice.

Citalopram hydrobromide is available in a liquid formulation, allowing for small dosage adjustments. Potential advantages for citalopram include greater specificity at the serotonin transporter, reduced drug-drug interactions via the cytochrome p450 isozymes,<sup>16</sup> and a favorable half-life compared with other members from this class.<sup>17</sup> Preliminary data from open trials show promising results for citalopram.<sup>18,19</sup>

The National Institutes of Health–sponsored Studies to Advance Autism Research and Treatment (STAART) network undertook a placebo-controlled trial of citalopram for repetitive behavior in children with ASDs. We hypothesized that treatment with citalopram would improve global functioning by reducing repetitive behavior. We also predicted that the use of a low starting dosage, followed by gradual upward adjustment, would identify an effective well-tolerated dosage range with few adverse events.

## METHODS

The trial, NCT00086645, was registered at [clinicaltrials.gov](http://clinicaltrials.gov) before initiation and was conducted at the following 6 academic medical centers: Mount Sinai School of Medicine, New York, New York;

North Shore–Long Island Jewish Health System, New York; University of North Carolina at Chapel Hill; University of California at Los Angeles; Yale University, New Haven, Connecticut; and Dartmouth Medical School, Hanover, New Hampshire. Each site's institutional review board approved the study. At least 1 parent or guardian for each participant provided written informed consent, and subjects who were capable provided assent. The National Institute of Mental Health convened a Data and Safety Management Board that monitored the trial. Enrollment began on April 1, 2004, and was completed on October 31, 2006.

## PARTICIPANTS

Subjects were required to be 5 to 17 years old; meet *DSM-IV-TR* criteria for autistic disorder, Asperger disorder, or pervasive developmental disorder, not otherwise specified, as determined by an experienced clinician and as informed by the Autism Diagnostic Interview–Revised<sup>20</sup> and the Autism Diagnostic Observation Schedule<sup>21</sup>; have an illness severity rating of at least moderate on the Clinical Global Impressions, Severity of Illness Scale; and score at least moderate on compulsive behaviors ( $\geq 8$  on the sum of items 1A, 2, 3, and 5) measured with the Children's Yale-Brown Obsessive Compulsive Scales modified for pervasive developmental disorders (CYBOCS-PDD).<sup>22</sup> To address the generalizability of study outcomes, information on participant race/ethnicity was elicited by self-categorization as American Indian or Alaskan native, Asian, black, native Hawaiian, white, Hispanic, or other.

Subjects were excluded if they had the following: Rett disorder or childhood disintegrative disorder, a seizure within the past 6 months, weight less than 15 kg, a medical condition that might interfere with study participation, clinically significant abnormal baseline laboratory test results, history of adverse events or failed treatment while taking 2 or more SSRIs, prior treatment with citalopram or escitalopram oxalate, recent initiation of behavioral therapy, or history of bipolar disorder or manic episode.

The principal investigators reviewed potential subjects with complex medication histories before enrollment. Apart from sleep medication (melatonin or diphenhydramine hydrochloride), concomitant treatment with psychotropic medications or medication having known interactions with citalopram was not permitted.

## TREATMENT

Liquid citalopram (Celexa, 10 mg/5 mL) was obtained commercially. Placebo matched for smell, taste, and viscosity was prepared at each site's pharmacy according to study specifications.

## RANDOMIZATION AND BLINDING

Participants were randomly assigned to citalopram or placebo using permuted blocks with randomly varying block sizes stratified by site and by age (5-11 vs 12-17 years). Two masked clinicians met with participants during each scheduled evaluation. The evaluating clinician monitored efficacy and was blinded to adverse events. The treating clinician reviewed efficacy ratings, monitored and recorded adverse events, and subsequently adjusted the medication dosage as clinically indicated.

## DOSING

All participants began with 2.5 mg/d. The maximal dosage was 20 mg/d. For children weighing less than 40 kg, dosage increases were restricted to 2.5-mg increments until day 43 and were increased biweekly in 5-mg increments thereafter. For children weighing at least 40 kg, 2.5-mg dosage increases were allowed at weekly intervals until day 36 and were allowed to increase by 5 mg biweekly thereafter. The dosage schedule was followed unless the score on

the Clinical Global Impressions, Improvement Scale (CGI-I) was rated much improved or very much improved by the evaluating clinician. If the treating clinician suspected a dose-limiting adverse effect, the dosage could be lowered in 2.5-mg increments. Compliance was assessed by diary and by medication returned.

## EFFICACY MEASURES

The primary outcome measure was the CGI-I rated by the evaluating clinician. The CGI-I is a subscale scored from 1 (very much improved) to 7 (very much worse).<sup>23</sup> A score of 4 reflects no change. Positive response was defined by a score of 2 (much improved) or 1 (very much improved) at week 12. The following 8 secondary outcomes were evaluated: the CYBOCS-PDD, a composite measure of the CGI-I and the CYBOCS-PDD (CGI-I score of 1 or 2 and a 25% reduction on the CYBOCS-PDD), and 6 subscales of the Repetitive Behavior Scale. The CYBOCS-PDD, which was rated by the evaluating clinician, is designed to measure the severity of repetitive behavior in children with ASDs.<sup>22</sup> The 5 items (time spent, interference, distress, resistance, and control) are rated from 0 (least severe) to 4 (most severe); a higher score indicates more severe repetitive behavior. The parent-rated Repetitive Behavior Scale-Revised comprises 43 items across 6 subscales rated from 0 (not present) to 3 (severe).<sup>24</sup> The Aberrant Behavior Checklist-Community version<sup>25,26</sup> measures inappropriate behavior on a 4-point severity scale, where 0 indicates not a problem at all and 3 indicates a severe problem. The Aberrant Behavior Checklist-Community version contains 5 subscales (Irritability, Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech) and has been commonly used as an outcome measure in clinical trials among children with autism.<sup>27-30</sup> Evaluating clinicians from all sites were trained to reliability on the CYBOCS-PDD, CGI-I, and Clinical Global Impressions, Severity of Illness Scale at the beginning and midpoint of the trial. Training on the Clinical Global Impressions scale resulted in excellent interrater reliability, with 95% to 100% agreement to within 1 U of a gold standard rating on 5 vignettes established by 2 expert raters (B.H.K. and L. Scahill). The CYBOCS-PDD training included a review of the instrument and co-rating of 3 video-recorded interviews. All raters achieved the criterion of within 2 points of the gold standard established by an expert rater.

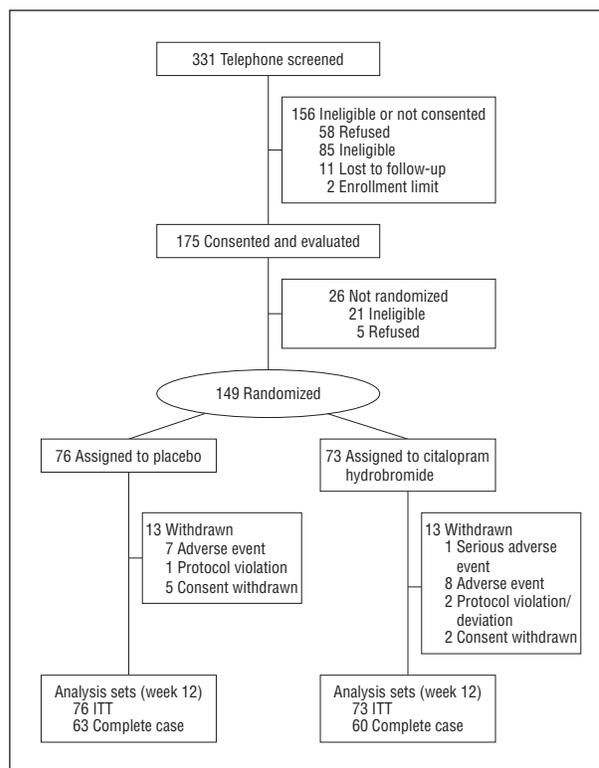
## SAFETY MEASURES

Treatment-emergent adverse events were elicited at each bi-weekly visit by the treating clinician using the Safety Monitoring Uniform Report Form, a semistructured review of body systems.<sup>31</sup> Vital signs (pulse and blood pressure) and weight were measured at each visit. Blood samples for complete blood cell count, electrolyte levels, liver functions, and citalopram and serotonin levels were obtained at week 12.

## STATISTICAL ANALYSIS

Subject disposition from screening to week 12 was described with frequencies and percentages. All efficacy and safety analyses used the intent-to-treat principle. Tests for differences in means of continuous variables were performed using 2 independent-samples *t* tests, and differences in distributions of categorical variables were assessed using the Fisher exact test or  $\chi^2$  test. Multiple linear and logistic regression analyses were used to assess interaction by clinical center and the effect of other potential covariates, confounders, and effect modifiers, including medication adherence and dosage. Generalized estimating equations were used to evaluate the effect of treatment in outcomes measured successively over time.

The primary analysis compared the proportion of subjects showing a positive response between groups using the  $\chi^2$  test. For



**Figure 1.** Consolidated Standards for Reporting of Trials (CONSORT) chart. ITT indicates intent to treat.

subjects who failed to complete all postrandomization assessments, the last observation was carried forward. For comparison purposes, analyses were also performed among subjects who completed all assessments. A similar approach was followed for each secondary outcome. All analyses are performed using commercially available software (SAS version 9.1; SAS Institute, Cary, North Carolina). Unless otherwise specified, all statistical tests were performed at a 5% level of significance (2-sided).

The study was designed to ensure 90% power to detect a relative risk of 2.25 (eg, 45% vs 20% of subjects meeting response criteria for the primary outcome in the citalopram and placebo groups, respectively) using a 2-sided  $\chi^2$  test at a 5% level of significance. The outcome used to determine size was the composite criterion (CGI-I score of 1 or 2 and a 25% reduction on the CYBOCS-PDD). This sample size calculation ensured sufficient power for the primary and main secondary analyses.

## RESULTS

Two hundred forty-four of 331 participants screened by telephone were presumed eligible and were invited for a screening visit. Consent was obtained for 175 subjects, and 149 were randomized to receive citalopram ( $n=73$ ) or placebo ( $n=76$ ). Most participants (82.6%) completed the 12-week trial. In the citalopram-treated group, 12.3% stopped early due to adverse events and another 2.7% withdrew consent; in the placebo group, 9.2% left early owing to adverse events and another 6.6% withdrew consent (**Figure 1**). The citalopram-treated and placebo groups were balanced in terms of demographic and baseline characteristics, including age, sex, race/ethnicity, nonverbal IQ, Tanner stage, and Clinical Global Impressions, Severity of Illness Scale score (**Table 1**).

**Table 1. Demographics and Baseline Characteristics by Treatment Group**

Characteristic	Citalopram Hydrobromide-Treated Group (n=73)	Placebo Group (n=76)
Age at consent, y		
Mean (SD)	9.1 (3.2)	9.6 (3.1)
Median	8.6	9
Minimum-maximum	5.0-17.3	5.1-17.1
Nonverbal IQ >70, No. (%) <sup>a</sup>	43 (61.4)	43 (60.6)
CGI severity score, No. (%)		
4 Moderately ill	21 (28.8)	22 (28.9)
5 Markedly ill	37 (50.7)	37 (48.7)
6 Severely ill	14 (19.2)	16 (21.1)
7 Among the most extreme	1 (1.4)	1 (1.3)
Male sex, No. (%)	64 (87.7)	64 (84.2)
Hispanic race/ethnicity, No. (%) <sup>b</sup>	9 (12.5)	8 (10.5)
Race/ethnicity, No. (%) <sup>c</sup>		
American Indian or Alaskan native	0	2 (2.6)
Asian	6 (8.2)	8 (10.5)
Black	7 (9.6)	10 (13.2)
Native Hawaiian	1 (1.4)	0
White	53 (72.6)	55 (72.4)
Other	6 (8.2)	4 (5.3)
Tanner stage, No. (%) <sup>d</sup>		
1	52 (73.2)	48 (63.2)
2	10 (14.1)	12 (15.8)
>3	9 (12.7)	16 (21.1)

Abbreviation: CGI, Clinical Global Impressions, Severity of Illness Scale.

<sup>a</sup>Assessments were not collected for 8 participants (3 from the citalopram group and 5 from the placebo group). IQ was assessed as follows: Leiter-revised (71 [47.7%]), Wechsler Intelligence Scale for Children-IV (36 [24.2%]), Wechsler Abbreviation Scale of Intelligence (17 [11.4%]), Mullen (15 [10.1%]), Stanford Binet (2 [1.3%]), and untested (8 [5.4%]).

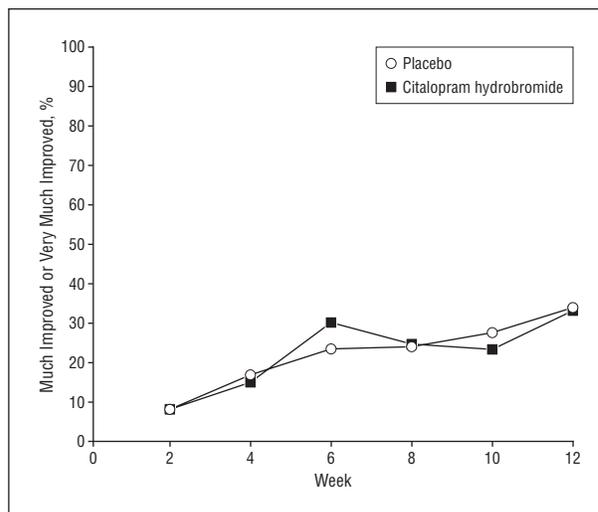
<sup>b</sup>One subject in the citalopram group is missing race/ethnicity.

<sup>c</sup>Subjects can designate more than 1 race/ethnicity. Race/ethnicity is missing for 4 subjects in the citalopram group and for 2 subjects in the placebo group.

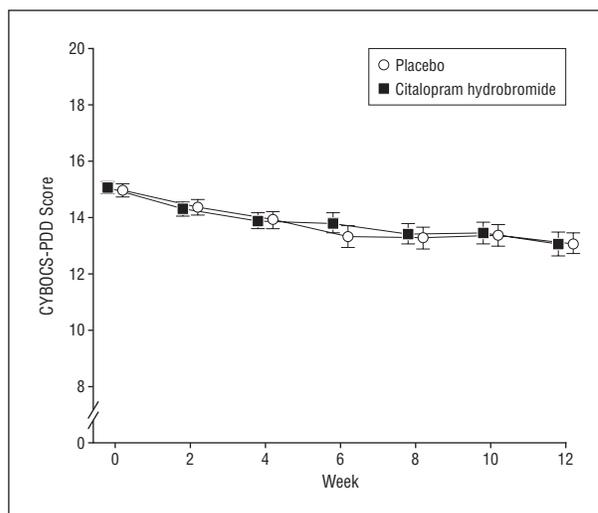
<sup>d</sup>Two subjects in the citalopram group are missing Tanner stage.

## EFFICACY

There was no significant difference in the proportion of CGI-I responders at 12 weeks between the citalopram-treated group (32.9%) and the placebo group (34.2%) (relative risk, 0.96; 95% confidence interval, 0.61-1.51;  $P > .99$ ). Using the generalized estimating equation method, although there was significant improvement for participants over time ( $P < .001$ ), there was no significant difference in the rate of improvement on the CGI-I between the groups ( $P = .94$ ) (**Figure 2**). Over time, there was no significant difference between the groups in score reduction on the CYBOCS-PDD from baseline (mean [SD],  $-2.0$  [3.4] points [from 15.1 to 13.1 points] for the citalopram group and  $-1.9$  [2.5] points [from 15.0 to 13.1 points] for the placebo group;  $P = .85$ ) (**Figure 3**). Increasing the threshold for positive response by using the combined CGI-I and CYBOCS-PDD criteria also showed no difference between treatment groups at 12 weeks (20.6% for citalopram vs 13.2% for placebo;  $P = .28$ ). Furthermore, there were no significant differences in any of the 6 subscale scores of the Repetitive Behavior Scale-Revised at 12 weeks ( $P > .37$  for all) (**Table 2**). Although the change in the Irritability



**Figure 2.** Percentage of children with a rating of much improved or very much improved on the Clinical Global Impressions, Improvement subscale during the 12-week trial. All children assigned to citalopram hydrobromide (n=73) and to placebo (n=76) are included. Week 2 is the first opportunity to assess change from baseline. Using the generalized estimating equation method, there was no statistical difference between groups over time.



**Figure 3.** The mean scores on the Children's Yale-Brown Obsessive Compulsive Scales modified for pervasive developmental disorders (CYBOCS-PDD) over time. Scores reflect frequency and intensity of repetitive behaviors and are shown with the standard error. All children assigned to citalopram hydrobromide (n=73) and to placebo (n=76) are included. Using the generalized estimating equation method, there was no statistical difference between groups over time.

subscale score of the Aberrant Behavior Checklist-Community version achieved statistical significance (without any correction for multiple comparisons) from baseline to week 12 (Table 2), the difference in change scores was small (2.27 points favoring the citalopram group). None of the other Aberrant Behavior Checklist-Community version subscale scores differed by treatment group. The results for the primary and secondary outcomes remained consistent when adjusted for dosage, adherence, and relevant baseline characteristics. The results of complete case analyses were also consistent with the lack of any meaningful differences between the active and placebo treatment arms. There was no significant effect of IQ on treatment response.

**Table 2. Compulsive and Repetitive Behaviors Over Time in the Trial by Treatment Group**

Variable	Citalopram Hydrobromide, Mean (SD)			Placebo, Mean (SD)			Difference in Change Scores (95% CI)	P Value
	Baseline	End Point	Change	Baseline	End Point	Change		
CYBOCS-PDD score	15.1 (1.8)	13.1 (3.7)	-2.0 (3.4)	15.0 (2.1)	13.1 (3.2)	-1.9 (2.5)	-0.1 (-1.1 to 0.9)	.81
RBS-R score								
Compulsive	7.0 (5.4)	5.2 (4.4)	-1.8 (3.9)	5.9 (4.3)	4.8 (4.1)	-1.3 (3.2)	-0.5 (-1.7 to 0.6)	.37
Restrictive	4.7 (2.8)	4.2 (3.1)	-0.6 (2.6)	4.1 (3.0)	3.2 (2.8)	-0.9 (2.5)	0.3 (-0.6 to 1.1)	.53
Ritualistic	7.0 (4.8)	5.3 (3.8)	-1.6 (3.5)	6.9 (4.5)	5.3 (4.4)	-1.5 (3.4)	-0.1 (-1.2 to 1.1)	.92
Sameness	11.2 (7.4)	8.1 (6.5)	-3.0 (6.0)	10.2 (6.9)	7.8 (6.2)	-2.4 (5.3)	-0.7 (-2.5 to 1.2)	.48
Self-injurious	2.8 (3.0)	2.4 (2.7)	-0.4 (3.0)	2.6 (2.6)	2.0 (2.6)	-0.7 (2.0)	0.3 (-0.6 to 1.1)	.55
Stereotyped	6.8 (4.0)	5.5 (4.0)	-1.2 (3.2)	6.1 (3.9)	5.0 (3.9)	-1.1 (2.7)	-0.2 (-1.1 to 0.8)	.75
ABC-CV score								
Irritability	13.2 (8.8)	10.1 (9.3)	-3.2 (6.5)	11.2 (8.5)	10.2 (8.9)	-0.9 (6.0)	-2.27 (-4.3 to -0.2)	.03
Social withdrawal	11.4 (8.2)	8.1 (8.1)	-3.4 (6.1)	11.1 (8.0)	8.2 (7.5)	-2.9 (5.0)	-0.49 (-2.3 to 1.3)	.60
Hyperactivity	20.2 (11.7)	18.5 (12.9)	-1.6 (7.8)	20.2 (11.2)	17.4 (11.5)	-3.1 (7.8)	1.53 (-1.0 to 4.1)	.24
Stereotypy	7.2 (4.8)	6.47 (5.5)	-0.7 (4.5)	7.2 (4.5)	6.2 (4.8)	-1.0 (3.3)	0.37 (-0.9 to 1.7)	.57
Inappropriate speech	5.3 (3.7)	4.4 (3.7)	-0.8 (2.9)	5.0 (3.7)	4.2 (3.3)	-0.8 (2.5)	-0.04 (-0.9 to 0.8)	.93

Abbreviations: ABC-CV, Aberrant Behavior Checklist–Community version; CI, confidence interval; CYBOCS-PDD, Children's Yale-Brown Obsessive Compulsive Scales modified for pervasive developmental disorders; RBS-R, Repetitive Behavior Scale–Revised.

### CITALOPRAM LEVELS

The mean (SD) dosages of citalopram hydrobromide and placebo at week 12 were 16.5 (6.5) mg (mode, 20 mg) and 18.5 (3.5) mg (mode, 20 mg), respectively ( $P = .05$ ). In the citalopram-treated group, the drug level at 12 weeks ranged from 0 to 260 ng/mL (mean [SD], 55.7 [49.3] ng/mL). The zero value was obtained from a child who dropped out of the study early in the trial but returned for his scheduled 12-week visit, consistent with intent-to-treat principles. Parent-reported adherence to treatment was high in both groups (mean [SD], 96.1% [7.8%] for the citalopram-treated group and 98.6% [3.1%] for the placebo group;  $P = .03$ ).

### ADVERSE EVENTS

Compared with placebo, adverse events were significantly more likely to occur in the citalopram-treated group, in which 97.3% subjects (vs 86.8% in the placebo group) reported at least 1 treatment-emergent adverse events ( $P = .03$ ). The most common adverse events in the citalopram-treated group were increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypy, diarrhea, insomnia, and dry skin or pruritus. **Table 3** provides the numbers and percentages for events occurring at a threshold of at least 10% of the subjects in either group. Although not listed in Table 3, nightmares occurred in 6.8% of the citalopram-treated group and in 0% of the placebo group ( $P = .03$ ). Two subjects (2.7%) treated with citalopram experienced seizures during the trial. One subject with a history of seizures had a single seizure and continued in the trial with the addition of an anticonvulsant medication. The other subject had a serious adverse event consisting of a prolonged seizure with loss of consciousness, and required emergency hospitalization. Although citalopram treatment was stopped, the subject subsequently continued to have frequent seizures.

### COMMENT

Citalopram was not superior to placebo in this sample of children with ASDs. Neither the rate of positive global response to citalopram treatment, nor the dimensional scores of repetitive behavior on the blinded clinician-rated CYBOCS-PDD, nor the parent-rated Repetitive Behavior Scale–Revised scores suggested any difference between groups. Although a difference emerged between treatment groups on the Irritability subscale score of the Aberrant Behavior Checklist–Community version, this difference does not seem to be clinically meaningful, and absolute end point values were equivalent.

The absence of an effect with citalopram is unlikely owing to attrition, inadequate sample size, or poor adherence to the protocol, as most of the participants completed the entire trial and because treatment compliance was excellent. Another potential explanation for the failure of citalopram to differentiate from placebo in our study is inadequate dosing (maximum, 20 mg/d). Although possible, the citalopram dosage schedule used in the trial was associated with significantly elevated rates of adverse events, suggesting that further dosage increases would not have been advised. In addition, we found no relationship between citalopram dosage or measured citalopram level and clinical response. The mean maximum dosage achieved, 16.5 mg/d, is similar to dosages identified as effective in open-label studies of ASDs.<sup>18,19</sup> In the open-label study of escitalopram by Owley et al,<sup>32</sup> 40% of responders were treated with dosages well within this range (<10 mg/d of escitalopram oxalate). Furthermore, our measured citalopram levels at week 12 (mean [SD], 55.7 [49.3] ng/mL) exceed those reported for adults receiving 20 mg/d for depression.<sup>33</sup> Therefore, underdosing is an unlikely explanation for our results.

A potential limitation of this study is the selection of repetitive behavior as the major treatment focus. The rationale for this target is the established efficacy of SSRIs for reducing symptoms of obsessive-compulsive disorder in children and adolescents.<sup>34,35</sup> However, it may be

**Table 3. Adverse Events Elicited During the Trial by Treatment Group**

Adverse Event <sup>a</sup>	No. (%)		P Value <sup>b</sup>
	Citalopram Hydrobromide–Treated Group (n=73)	Placebo Group (n=76)	
Any adverse event	71 (97.3)	66 (86.8)	.03
<b>Neuropsychiatric Disorders</b>			
Energy level increased	28 (38.4)	15 (19.7)	.02
Anger or irritability	18 (24.7)	13 (17.1)	.31
Aggression or hostility	17 (23.3)	13 (17.1)	.42
Headache or migraine	15 (20.5)	10 (13.2)	.28
Restlessness or difficulty settling down	13 (17.8)	7 (9.2)	.15
Disinhibited, impulsive, or intrusive behavior	14 (19.2)	5 (6.6)	.03
Silliness	9 (12.3)	10 (13.2)	>.99
Anxiety	8 (11.0)	9 (11.8)	>.99
Mood lability	7 (9.6)	9 (11.8)	.79
Increased speech	8 (11.0)	4 (5.3)	.24
Attention and concentration decreased	9 (12.3)	2 (2.6)	.03
Hyperactivity	9 (12.3)	2 (2.6)	.03
Stereotypy	8 (11.0)	1 (1.3)	.02
<b>Gastrointestinal Disorders</b>			
Diarrhea or loose stools	19 (26.0)	9 (11.8)	.04
Abdominal discomfort	13 (17.8)	9 (11.8)	.36
Vomiting or nausea	14 (19.2)	6 (7.9)	.06
<b>Sleep Disturbance</b>			
Any insomnia	28 (38.4)	17 (22.4)	.05
Insomnia, initial or difficulty falling asleep	17 (23.3)	7 (9.2)	.03
Insomnia, midcycle or other	13 (17.8)	9 (11.8)	.36
<b>Infections and Infestations</b>			
Cold, flu, or other systemic infection	31 (42.5)	26 (34.2)	.32
<b>Metabolism and Nutrition Disorders</b>			
Appetite decreased	11 (15.1)	10 (13.2)	.82
Appetite increased	7 (9.6)	8 (10.5)	>.99
<b>Skin and Subcutaneous Tissue Disorders</b>			
Rash	12 (16.4)	8 (10.5)	.34
Other skin or subcutaneous tissue disorder	9 (12.3)	1 (1.3)	.01
<b>General Disorders</b>			
Fatigue	10 (13.7)	10 (13.2)	>.99
<b>Immune System Disorders</b>			
Allergies	15 (20.5)	11 (14.5)	.39
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>			
Cough	10 (13.7)	5 (6.6)	.18
<b>Serious Events</b>			
Any serious adverse event	1 (1.4)	0	.49

<sup>a</sup> Adverse events with at least 10% occurrence in 1 or both groups, excluding adverse events present at baseline.

<sup>b</sup> Italics indicate statistical significance.

that the repetitive behavior in children with ASDs is fundamentally different from what is observed among children with obsessive-compulsive disorder in its behavioral picture and in its biologic underpinnings.<sup>22</sup>

A strength of the use of a global measure of response (eg, not restricted to repetitive behavior) is that clinically meaningful improvement associated with medication use was unlikely to be missed. Therefore, this approach provided the opportunity to detect benefits in areas other than repetitive behavior. It is possible that the outcome would have been different had there been a specific recruitment threshold established for other potential targets (eg, anxiety, irritability, and mood symptoms). Ratings on the Aberrant Behavior Checklist, Irritability subscale at entry in this study averaged 13 points. This total is half that of subjects in the Research Units on Pediatric Psychopharmacology risperidone study,<sup>36</sup> in which irritability was a specific focus of treatment. Therefore, we cannot rule out the possibility that citalopram could be effective for these other treatment targets. On the other hand, it is also possible that citalopram-responsive symptoms are simply uncommon and went undetected on the CGI-I in this large sample.

The overall rate of adverse events observed across groups in this trial may seem high, perhaps owing to the systematic method of elicitation used in the trial.<sup>31</sup> Although few adverse events led to discontinuation, citalopram use was associated with significantly more adverse events than placebo. The frequent observation of increased energy level, insomnia, and impulsiveness with citalopram therapy is consistent with many reports concerning the emergence of behavioral problems in children having ASDs treated with SSRIs. The finding of stereotypy as an adverse event with a drug that was hypothesized to help repetitive behavior was unexpected and did not seem to be associated with general behavioral activation, as this symptom did not significantly co-occur with increased energy level or impulsiveness. It is possible that an increase in stereotypy may be a proxy for some other nonspecific discomfort. Two children experienced convulsions while treated with citalopram. It is unclear whether citalopram use was causal, as one child had a preexisting seizure disorder and the other child continued to experience seizures after discontinuation of the drug. However, these events are consistent with some reports of an association of SSRIs and seizures (eg, in overdose).<sup>37</sup> This highlights the importance of clinical discussion and monitoring for emergence or worsening of convulsions in vulnerable populations. Together, the results of this trial highlight that SSRI exposure in children with ASDs is not without risk.<sup>14,38-40</sup>

Our placebo response rate of 34.2% is consistent with some other studies<sup>41,42</sup> involving children with autism and other conditions such as depression. This reinforces the value of placebo control in pediatric psychopharmacologic research.

The contrast between the published positive open-trial citalopram experience<sup>18,19</sup> and this negative large controlled study might raise questions about the efficacy of SSRIs as a class for repetitive behavior in childhood ASDs. In a controlled trial of the SSRI fluvoxamine, a low response rate (6%) and poor tolerability were also reported.<sup>14</sup> In contrast, the small trial by Hollander et al<sup>8</sup> showed that low-dose fluoxetine treatment was modestly but statistically beneficial for repetitive behavior in childhood ASDs and was well tolerated. Although there may be differences in response to particular SSRIs among this population, at present there is insufficient research evidence to merit a clear recommendation regarding the

use of SSRIs as a class for the treatment of repetitive behaviors in children with ASDs.

There is growing recognition that children and adolescents with ASDs have serious behavioral problems and psychiatric symptoms that may be appropriate targets for pharmacotherapy.<sup>7,43</sup> To date, there are few large-scale trials to guide clinical practice, so clinicians are left to address these problems with inadequate information. The results of this trial indicate that citalopram is not an effective treatment for children having ASDs with moderate or greater repetitive behavior. The results also highlight the urgent need for placebo-controlled trials of medications commonly used for children with ASDs to determine whether the risks of specific drugs substantially outweigh their benefits.

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