Neuropsychopharmacology (2005) 30, 582–589

www.neuropsychopharmacology.org

A Placebo Controlled Crossover Trial of Liquid Fluoxetine on Repetitive Behaviors in Childhood and Adolescent Autism

Eric Hollander*[,1,2], Ann Phillips[1,2], William Chaplin[1,2], Karen Zagursky[1,2], Sherie Novotny[1,2], Stacey Wasserman[1,2] and Rupa Iyengar[1,2]

[1]Seaver and New York Autism Center of Excellence, New York, USA; [2]Department of Psychiatry, Mount Sinai School of Medicine, One Gustave L Levy Place, New York, USA

Repetitive behaviors are a core symptom domain in autism that has been linked to alterations in the serotonin system. While the selective serotonin-receptive inhibitor fluvoxamine has been shown to be effective in adults with autism, as yet no published placebo controlled trials with these agents document safety and efficacy in children with autism. This study examines the selective serotonin reuptake inhibitor liquid fluoxetine in the treatment of repetitive behaviors in childhood and adolescent autism spectrum disorders (ASDs). In total, 45 child or adolescent patients with ASD were randomized into two acute 8-week phases in a double-blind placebo-controlled crossover study of liquid fluoxetine. Study design included two randomized 8-week fluoxetine and placebo phases separated by a 4-week washout phase. Outcome measures included measures of repetitive behaviors and global improvement. Low-dose liquid fluoxetine (mean final dose: 9.9 ± 4.35 mg/day) was superior to placebo in the treatment of repetitive behaviors by CY-BOCS compulsion scale. The effect size was in the moderate to large range, and the doses used were low. Liquid fluoxetine was only slightly, and not significantly, superior to placebo on CGI autism score partially due to a phase order effect. However, fluoxetine was marginally superior to placebo on a composite measure of global effectiveness. Liquid fluoxetine did not significantly differ from placebo on treatment emergent side effects. Liquid fluoxetine in low doses is more effective than placebo in the treatment of repetitive behaviors in childhood autism. Limitations include small sample size and the crossover design of the study. Further replication and long-term maintenance trials are needed.

Neuropsychopharmacology (2005) **30,** 582–589, advance online publication, 15 December 2004; doi:10.1038/sj.npp.1300627

Keywords: autism; fluoxetine; repetitive behaviors; OCD

INTRODUCTION

Autism is a developmental disorder of unknown etiology that has a major impact on individuals with the disorder, their families, and society. While there is a great need to find medications that can help treat core and secondary symptoms, to date there are no medication treatments approved by the Food & Drug Administration (FDA) for use in autism (Hollander *et al*, 2003b).

The core features of autism include difficulties with social interaction, communication, and compulsive/repetitive behaviors but other associated problem behaviors occur within the autistic syndrome (ie attentional difficulties, self-injurious behavior, mental retardation, stereotypy, affective instability, and seizures). These symptoms themselves cut across a number of disorders. Thus, it is possible to make progress in understanding autism by investigating commonalities between core symptoms in autism and similar symptoms in other disorders. Targeted treatment approaches in autism focus on treating symptom domains, and utilizing treatments that have been efficacious in treating similar symptoms in other disorders (Hollander *et al*, 2003b). For instance, there is some similarity between the repetitive behaviors seen in autism and behaviors seen in obsessive-compulsive disorder. Selective serotonin reuptake inhibitors (SSRIs), which improve repetitive behaviors in obsessive-compulsive disorder (Tollefson *et al*, 1994; Greist *et al*, 1995; Clomipramine Collaborative Study Group, 1991; Hollander *et al*, 2003a) might also be utilized to target this symptom domain in autism. However, whether or not the repetitive/stereotypic behaviors associated with autism represent a similar behavioral dimension to the compulsive symptoms of OCD is still uncertain. In both cases, while the primary focus is treating repetitive behaviors, the treatment effect may also improve other symptom domains either directly or indirectly.

Trials with SSRIs suggest benefits in adults with autism spectrum disorders (ASDs). In the only double-blind study

*Correspondence: Dr E Hollander, Department of Psychiatry, The Mount Sinai School of Medicine, Box 1230, One Gustave L Levy Place, New York, NY 10029, USA, Tel: +1 212 241 3623, Fax: +1 212 987 4031, E-mail: eric.hollander@mssm.edu
Received 11 March 2004; revised 28 September 2004; accepted 21 October 2004
Online publication: 1 November 2004 at http://www.acnp.org/citations/Npp11010404011 5/default.pdf

of an SSRI in adult autism to date, McDougle *et al* (1996b) conducted a placebo-controlled study of fluvoxamine and found that 8/15 (53%) patients were responders compared to 0/15 in the placebo group. Significant improvements in repetitive thoughts and behavior, maladaptive behavior, aggression, social relatedness and language usage were reported. In contrast to this adult trial of fluvoxamine, a subsequent trial in children and adolescents with ASD conducted by the same group found poor response to fluvoxamine, only one of 18 responded, while 14 had adverse effects (McDougle *et al*, 2000). However, subjects were started on a relatively high dose of 50 mg, which may have contributed to early activation symptoms that limited tolerability.

It is also unknown whether this variability in tolerability and treatment response between children and adults in the autistic population is unique to fluvoxamine or extends to other SSRIs. Several studies suggested that children may respond better to low doses of SSRIs, specifically fluoxetine, than they did to fluvoxamine. Preliminary open-label trials and observations have demonstrated alleviation of autistic symptoms with fluoxetine for both adults and children (Fatemi *et al*, 1998; Markowitz, 1992). In the largest open label retrospective study of fluoxetine, DeLong *et al* (2002) found that 69% of 129 children aged 2–8 showed improvement on fluoxetine. Similarly, open-label trials of citalopram suggest the efficacy of this SSRI for the treatment of autistic symptoms as well (Namerow *et al*, 2003). Together, these open-label and retrospective studies suggest that fluoxetine may be useful for the treatment of children and adolescents with autism. Therefore, it is important to test the efficacy of fluoxetine in the context of a double-blind, placebo-controlled study.

Another reason to predict that SRIs may be efficacious in treating autism is evidence that serotonin (5-HT) has been implicated in the pathophysiology of autism (Cook and Leventhal, 1996). Several studies indicate specific brain regions that have altered 5-HT function in individuals with autism. A PET imaging study that utilized the radiolabeled 5-HT precursor alpha C^{11} methyl tryptophan, a tracer for 5-HT synthesis, found decreased 5-HT synthesis in frontal and thalamic regions and increased 5-HT synthesis in contralateral cerebellar dentate regions (Chugani *et al*, 1997). This finding is consistent with findings of increased inhibitory $5\text{-HT}_{1\text{dbeta}}$ sensitivity as measured by GH response to sumatriptan in adult autistic patients (Hollander *et al*, 2000; Novotny *et al*, 2000), since these receptors are prevalent in frontal and thalamic, but not cerebellar regions (Pascual *et al*, 1996). It is conceivable that SSRIs, which decrease the clearance of synaptic 5-HT, may exert their effect in autism by downregulating inhibitory $5\text{-HT}_{1\text{dbeta}}$ autoreceptors, thereby increasing the availability of synaptic 5-HT.

Disruption in the 5-HT system may be linked in particular with the repetitive behavior domain in autism. For instance, the acute depletion of the 5-HT precursor, tryptophan, has been reported to exacerbate many repetitive behaviors in autistic subjects, in particular whirling, flapping, pacing, banging and hitting themselves, rocking and anxiety (McDougle *et al*, 1996a). We have found that sensitivity of the $5\text{-HT}_{1\text{D}}$ receptor (measured by growth hormone (GH) response to sumatriptan) is positively correlated with the severity of the repetitive behavior domain rather than the severity of the overall autistic symptom complex or the other symptom domains (Hollander *et al*, 2000). These findings indicate that the repetitive behavior domain may be particularly accessible to improvement with SSRI treatment.

We hypothesized that treatment with low-dose liquid fluoxetine in children and adolescents would result particularly in improvement in one core symptom domain of autism: the repetitive behaviors domain. We also hypothesized that fluoxetine might improve global autism severity, perhaps indirectly by reducing the interference caused by repetitive behaviors. Therefore, we looked for effects of liquid fluoxetine *vs* placebo on global severity of illness in autism, as well as for tolerability of the two treatments.

METHODS

Subjects

Subjects were eligible if they were between 5 and 17 years of age and met criteria for an ASD, which includes autism, Asperger Syndrome, and Pervasive Developmental Disorder, not otherwise specified (PDD-NOS) by Autism Diagnostic Interview (ADI-R), Autism Diagnostic Observation Schedule (ADOS-G) and DSM-IV TR diagnosis by psychiatric interview, which included gathering information about timing and quality of early language in order to differentiate between Aspergers and PDD-NOS. Even though we expected to see greatest reduction in the repetitive behavior domain, there was no CY-BOCS cutoff for inclusion in this study. Subjects who were responding well to previous interventions or had only mild global severity were not included. Exclusion criteria also included DSM-IV psychotic disorders, a history of seizures, and any clinically significant medical illness. Patients were free of psychiatric medications for 6 weeks prior to participation, and no concurrent psychotropic medications or cognitive behavioral therapies were allowed during the study. In total, 62 parents of subjects signed informed consent and 25% of the children and adolescents were assessed by an independent clinical evaluator as capable of giving assent. A total of 18 children were enrolled but not randomized because they failed to meet full enrollment criteria or were noncompliant. In total, 44 were randomized and 39 were included in the ITT data analysis (19 fluoxetine first/placebo second phase; 20 placebo first/fluoxetine second phase). Following randomization, three subjects were dropped due to noncompliance and one was dropped because of lack of efficacy, all prior to week 4. None of these subjects had received any postrandomization primary outcome CY-BOCS assessments; therefore, it was not possible to include them in the analysis. One additional subject was dropped from the study because of lost pharmacy records, which made it impossible to be certain of the subject's randomization condition.

Outcome Measures

Repetitive behaviors. Our primary outcome measure focused on repetitive behavior symptoms, using the

Children's Yale-Brown Obsessive-Compulsion Scale, compulsions subscale (CY-BOCS). The Obsessions and Compulsions Checklist (CY-BOCS O-C Checklist) (Goodman *et al*, 1989), which lists past and present occurrence of different OCD symptoms, was used at baseline to assess the range of obsessive-compulsive symptoms and to generate a list of symptoms that was then used as reference for the CY-BOCS. The CY-BOCS is a direct adaptation of the Y-BOCS modified for administration to young children by the substitution of simpler language for scale probes. Ratings followed an interview of both the child and caretaker and were only taken for the half of the scale that cover compulsions, since obsessions are often not present in autism, and are very difficult to assess in this population.

Global measures. Secondarily, we were also interested in improvement in global autistic severity, and assessed this in two ways. We measured global severity independent of our primary target of repetitive behaviors using the Clinical Global Improvement Scale Adapted to Global Autism (CGI-AD) Guy, 1976. In addition, we created a composite measure (Global Autism Composite Improvement Measure) that includes both our target behavior as well as other core symptoms (ie speech and reciprocal social interaction) less responsive to change. This is more reflective of how the CGI-AD was utilized in other studies specifically to focus on behaviors (Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2002), where targeted behaviors were included in global autism ratings. This composite utilized the CGI-AD and incorporated a measure of change in the target symptom of repetitive behavior based on the CY-BOCS. Specifically, we created a change score by subtracting the pre-test CY-BOCS from the post-test CY-BOCS. Negative values on this measure indicate a reduction in repetitive behaviors at post-test whereas positive scores indicate an increase. This raw change measure was then added to the CGI-AD measure to augment the overall change in autism severity considering the change in behavior targeted by liquid fluoxetine.

Measures of side effects. Side effects were reviewed with the parent/guardian and subject, if able to do so, at each visit by the treating psychiatrist. Side effects were measured with the use of the Fluoxetine Side Effects Checklist (FSEC). This checklist has 63 items and covers each major biological system, and thus enabled the study psychiatrist to query parents regarding potential side effects in a thorough and systematic manner.

Owing to concerns about agitation and suicidality, we also included the Suicidality Subscale of the Overt Aggression Scale-Modified (OAS-M). This subscale consists of three items: suicidal tendencies, intent of attempt, and medical lethality. Severity of an event receives a scaled score (higher score for more impulsive/aggressive behaviors) and is then multiplied by the frequency of this event for the week.

Procedure. After a preliminary phone screening, the parents of potential participants gave informed consent and children 8-year-old and older gave assent to participate in the study. Participants were then assessed in person by a study psychiatrist who assigned DSM-IV diagnoses. Diagnosis was achieved through a structured interview (ADI-R) and through direct observation (ADOS-G), as well as by clinician interview. The Vineland Adaptive Behavior Scale was used to assess level of adaptive functioning. Intellectual functioning of verbal patients was assessed by the Wechsler Preschool and Primary Intelligence Scale-Revised (WPPSI-R) (age 5–7), Wechsler Intelligence Scale for Children (WISC-III) (ages 7–16) or the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (age 17). Intellectual functioning of nonverbal patients was assessed by the Leiter International Performance Scale-Revised.

The study consisted of three treatment phases: randomized double-blind liquid fluoxetine or placebo trial for 8 weeks, followed by a 4-week washout period, followed by a 8-week double-blind, crossover trial. A flexible titration schedule based on weight, tolerability, and side effects was used. Dosage began with 2.5 mg/day of liquid fluoxetine each day for the first week, and then was titrated as indicated by the subject's symptoms and side effects based on weight for the next 2 weeks up to a maximum dose of 0.8 mg/kg/day (0.3 mg/kg for week 2, 0.5 mg/kg/day for week 3, and 0.8 mg/kg/day for weeks 4–8). Dose prescribed on day 28 (end of week 4) was maintained for the remainder of the 8-week phase unless indicated due to side effects, in which case the stable dose was lowered. Although titration follows a flexible schedule, and subjects unable to tolerate a minimum dose of 2.4 mg/day would have been dropped from the trial, no subjects had difficulty on this dosage.

To allow for a gradual titration of medication to a therapeutic level and close monitoring of side effects, subjects were monitored and assessed weekly by the treating physician, who was blind to treatment condition, during the first 4 weeks of each fluoxetine/placebo phase of the study. For the remainder of the trial, and during the washout period, patients were monitored every other week. Adverse effects were monitored via the clinician administered FSEC at every visit. In addition, all CY-BOCS and CGI-AD outcome assessments were completed by an independent evaluator (IE) who did not have access to side effect data and who was blind to treatment condition, at baseline and every 4 weeks throughout the study, until week 20 or termination.

Liquid fluoxetine has an elimination half-life of 2–3 days for the parent and 7–9 days for the metabolite. Thus, the 4-week washout period between phases does not allow for complete elimination of the metabolite. However, in choosing the 4-week washout (9.3 elimination half lives for the parent compound, 1.75 elimination half lives for the metabolite) we balanced the burden on the patient with the complete elimination of the metabolite.

Data Analysis

We used mixed regression models with observations nested within subjects (Hedeker and Gibbons, 1996) to test the hypothesis that fluoxetine would reduce repetitive behaviors in children and adolescents with autism. We used this approach rather than the more traditional repeated measures ANOVA for two reasons. First, according to the intent to treat approach, we included all subjects with any postrandomization assessments ($N = 39$), even those who did not complete both phases of the trial, and therefore we

have some missing data; however, the amount of missing data in this study was relatively small. In all, 34 subjects completed both phases with the exception of two subjects whose final primary outcome measures were taken at week 18 instead of week 20. Five subjects completed the first phase only; of these, three had fluoxetine and two had placebo. For our primary outcome measure, the CY-BOCS, out of 234 possible data points, 215 were collected. For the CGI-AD measure, there were 71 observations out of a possible 76. Mixed regression models base estimates on all available data using maximum likelihood estimation. Using repeated measures ANOVA only subjects with complete data are included with resulting loss of power and possible bias. Second, this crossover design used the same subjects in both the placebo and fluoxetine conditions, with half the subjects receiving fluoxetine first and half receiving placebo first. The use of the same subjects in all conditions creates statistical dependency that is accounted for in mixed regression models. These analyses were all performed for the IE ratings who remained blind to both drug condition and side effect information.

RESULTS

Basic Sample Description

A total of 39 subjects, 30 (76.9%) male and nine (23.1%) female, ranging in age from 5 to 16 years (mean 8.18 ± 3.04) were included in the analysis (see Table 1). In total, 23 of these subjects were mentally retarded. In total, 57% of the subjects were Caucasian, 23% Black, 15% Hispanic and 5% Asian. A total of 90% had a diagnosis of autism and 10% had a diagnosis of Asperger syndrome. On average, their IQ was 63.65 ± 27.9 (range 30–132), with baseline CY-BOCS-compulsion scores averaging 13.15 ± 2.75, range 8–18, and baseline Vineland Adaptive Behavior Scale averaging 46.56 ± 22.02, range 20–110. There were no significant differences on CY-BOCS baseline scores between the randomization groups ($t = 1.104$, df $= 37$, $p = 0.28$), and no significant differences on the Vineland between groups ($t = 0364$, df $= 30.353$, $p = 0.719$). The mean baseline CGI-AD severity rating was 4.61 ± 0.86 with a minimum score of 3 and a maximum score of 6. There were no significant differences in CGI-AD Severity scores between the two randomization treatment groups ($t = 0.290$, df $= 37$ $p = 0.77$) (Table 1).

The mean maximum dosage for fluoxetine was 10.6 ± 3.65 mg (range 4.8–20 mg), or 0.38 ± 0.97 mg/kg based on subject's weight, and the mean final dose for fluoxetine was 9.9 mg $\pm$ 4.35 (range 2.4–20 mg), or 0.36 ± 0.116 mg/kg. The mean maximum dosage for placebo was 11.1 ± 4.47 mg fluoxetine equivalents (range 4.8–30 mg), 0.4 ± 0.11 mg/kg, and the mean final dose for placebo was 10.8 ± 4.7 mg equivalents (range 4.8–30 mg), 0.36 ± 0.15 mg/kg. There was a significant correlation between age and dose, with older children getting higher doses ($r = 0.72$, $p < 0.001$ for placebo, and $r = 0.58$, $p < 0.001$ for fluoxetine).

Primary Analyses

For the IE CY-BOCS scores we specified a mixed model with six observations nested within the 39 subjects. Three of the observations (baseline, mid-treatment, post-treatment) were obtained from the subjects on placebo (TREAT $= 0$) and three were obtained from the subjects on fluoxetine (TREAT $= 1$). We fit a linear trend to the three measures using -0.707, 0, and 0.707 as trend coefficients. The critical test is the treatment by linear interaction that would indicate that the decrease in CY-BOCS scores across time is different for the subjects on placebo than on fluoxetine. Secondarily, we fit a quadratic trend to the data using 0.408, -0.816, 0.408 as trend coefficients, and also tested if this trend interacted with treatment condition.

We found significant direct effects for treatment ($z = -2.852$, standard error (SE) $= 0.246$, $p = 0.004$), the linear trend ($z = -2.433$, SE $= 0.207$, $p = 0.015$), and quadratic trend ($z = 2.352$, SE $= 0.206$, $p = 0.019$). Most crucially,

Table 1 Subject Characteristics

Characteristic	Total sample ($n = 39$)	Placebo/ fluoxetine ($n = 20$)	Fluoxetine/ placebo ($n = 19$)
Gender n (%)			
Male	30 (76.9%)	17 (85%)	13 (68.4%)
Female	9 (23.1%)	3 (15%)	6 (31.6%)
Age (years)			
Mean ($\pm$SD)	8.18 (3.0)	7.35	9.1 (3.7)
Range	5–16	5–12	5–16
Ethnicity			
Caucasian	22 (56.4%)	11 (55%)	11 (57.9%)
Asian	2 (5.1%)	1 (5%)	1 (5.3%)
Black	9 (2 3.1%)	5 (2 5%)	4 (21.1%)
Hispanic	6 (15.4%)	3 (15%)	3 (15.8%)
Diagnosis			
Autism	34 (87.2%)	1 7 (85%)	71 (89.5%)
Aspergers	5 (12.8%)	3 (15%)	2 (10.5%)
Clinical global impressions scale (by independent evaluator)			
Autism severity ($\pm$SD)	4.6 (0.9)	4.5 (0.84)	4.7 (0.9)
C-YBOCS (by independent evaluator)			
Mean[a] ($\pm$SD)	13.2 (2.7)	13.5 (2.9)	12.8 (2.6)
Range	8–18	8–18	8–16
IQ[a]			
Mean ($\pm$SD)	63.7 (27.9)	68.1 (26.7)	59.2 (29.1)
Range	30–132	30–111	33–132
Vineland adaptive behavior composite[a]			
Mean($\pm$SD)	46.6 (21.9)	47.9 (19.4)	45.1 (24.6)
Range	20–110	20–107	20–110

$p > 0.07$ for all comparisons.
[a]Total sample $n = 34$, and $n = 1$ 7 for both conditions.

we also obtained a significant linear trend × treatment interaction ($z = -2.075$, SE = 0.407, $p = 0.038$). We did not find a significant quadratic trend × treatment interaction ($z = 1.147$, SE = 0.405, $p = 0.251$). Finally, the significant linear × treatment interaction was not affected by the order in which the placebo and fluoxetine was administered to the subjects ($z = -0.504$, SE = 0.832, $p = 0.614$). Thus, the pattern of results suggests that the fluoxetine group was lower overall on the CY-BOCS and that there were general linear and quadratic trends in the data in both the placebo and fluoxetine conditions. However, the linear decrease was significantly greater in the fluoxetine than in the placebo condition, indicating a treatment effect.

These results are shown graphically in Figure 1 in which the values of the actual means and standard errors on the CY-BOCS are presented. Table 2 describes the means and standard deviations for both drug condition and phase order. Finally, we present the linear model with the parameter estimates in Eq. (1). We used this model to predict the scores for the subjects at post-test in both the Fluoxetine and Placebo conditions.

$$\begin{aligned} \text{CY-BOCS}' = & 12.77 + (-0.70)\text{TREAT} \\ & + (-0.094)\text{LINEAR} + (0.49)\text{QUAD} \\ & + (-0.84)\text{LINEAR}\times\text{TREAT}. \end{aligned} \quad (1)$$

The predicted post-treatment score for the subjects on Fluoxetine (11.6) is 1.3 units lower than the post-treatment score for subjects on Placebo (12.9). Dividing this difference by the square root of the residual variance (2.96) converts this difference into a standardized estimate of the effect size that is analogous to Cohen's *d* statistic because both *d* and our index reflect the size of the difference relative to error. However, our estimate takes advantage of the completely within-subjects crossover design and the mixed regression analyses that removes the effects of within-subject change and individual differences from the error term. This estimate of the effect size is 0.76, which is conventionally interpreted as a 'medium-to-large' effect.

Secondary Analyses

Repetitive behaviors in first half of trial. In a *post hoc* manner, we also performed a mixed models analysis on the CY-BOCS for just the first phase for all of the 39 subjects. This is less powerful than our primary test because it does not allow for using each subject as their own comparison. This analysis did not yield a significant effect of treatment condition ($z = -0.00400$, SE = 1.201, $p = 0.689$).

Global measures. We assessed the effect of treatment on the overall improvement in autistic symptoms in two different ways. First using the CGI-AD ratings from the IE to focus on global severity of autism independent of our target domain of repetitive behaviors (ie language, socialization). The results from this mixed regression analysis indicated a nonsignificant difference in the CGI-AD ratings obtained at

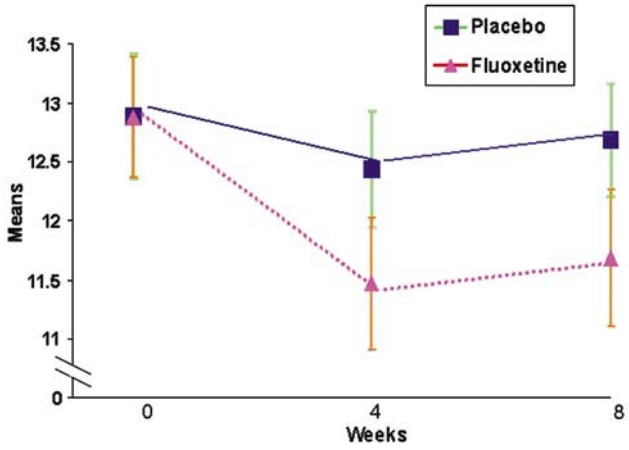

Figure 1 Effect of fluoxetine/placebo on repetitive behaviors (CY-BOCS Compulsion Score). Fluoxetine was superior to placebo on mean CY-BOCS with a linear trend by treatment interaction ($z = -2.075$, SE = 0.407, $p = 0.038$), as well as significant direct effects for treatment ($z = -2.852$, SE = 0.246, $p = 0.004$), linear trend ($z = -2.433$, SE = 0.207, $p = 0.015$), and quadratic trend ($z = 2.352$, SE = 0.206, $p = 0.019$).

Table 2 Means for Primary Outcome Measures

		Condition 1						Condition 2					
		Phase 1			Phase 2			Phase 1			Phase 2		
		Placebo			Fiuoxetine			Fiuoxetine			Placebo		
	Week	0	4	8	12	16	20	0	4	8	12	16	20
CY-BOCS	Mean	13.45	12.7	12.95	12.93	11.94	11.77	12.84	11.05	11.63	12.24	12.13	12.38
	SD	2.9	3.2	3.2	3.5	3.4	3.2	2.6	3.4	3.8	3.5	2.6	2.4
CGI-AD improvement	Mean			3.58			3.06			3.42			3.19
	SD			0.8			1.1			1.2			1
Global Comp improvement	Mean			3.21			1.73			2.21			3.50
	SD			2.6			3.6			3.0			3.0

post-treatment in the two conditions ($z = -0.645$, SE = 0.227, $p = 0.519$). However, there is some suggestion that these results were affected by the order in which the subjects experienced placebo or treatment. The test of the interaction of Treatment × Order yielded a z of 1.706 (SE = 0.438, $p = 0.088$). Specifically, it appears that subjects showed more improvement at their second post-treatment assessment, regardless of whether or not they were on placebo or fluoxetine. Figure 2 shows this Order × Treatment effect on the predicted CGI-AD scores.

Next, we also assessed treatment effects of fluoxetine on the post-test ratings of global composite autism that incorporates an index of change in repetitive behaviors. The results of this mixed regression analysis indicated a trend towards reduction in this global autism composite improvement measure for subjects on fluoxetine as compared to placebo ($z = -1.907$, SE = 0.703, $p = 0.056$). As shown in Figure 3, the subjects on fluoxetine had a reduction of −1.3 points (predicted score of 2.0 compared to a predicted score of 3.3 for placebo subjects) on this augmented autism severity index. Using the same approach that we used in the primary analyses, the standardized estimate of this effect is a moderate 0.46.

This global autism composite measure is composed of a CY-BOCS change measure and the CGI-AD measure. In order to analyze the relative contribution of each component to the composite score we performed a regression on the global composite for the two variables that make it up.

Standardized partial regression coefficients and semi-partial ('part') correlations indicate how much each measure contributes independently to the composite. The relative size of these two statistics are about the same 0.334 *vs* 0.878 or 0.328 *vs* 0.861 in favor of the CY-BOCS change measure. Thus, both measures contribute to the effect; however, the CY-BOCS contributes more than the CGI-AD measure.

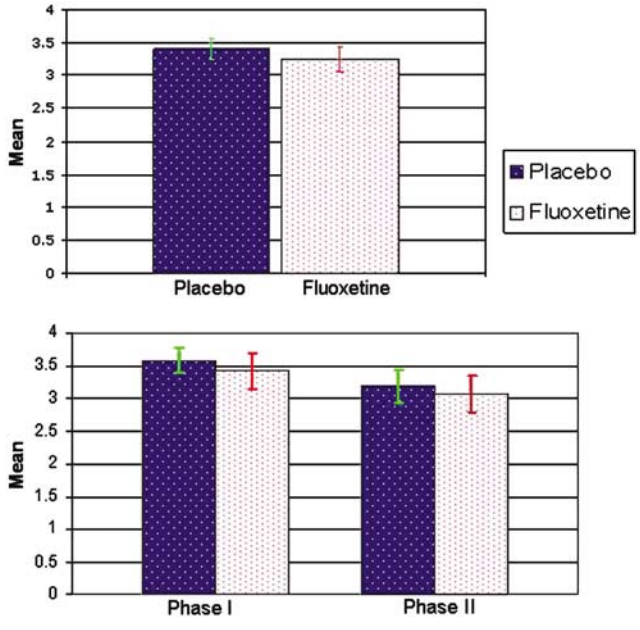

Figure 2 Effects of phase order and treatment condition on global CGI-AD improvement. There was an interaction of condition and treatment on the Global CGI-AD scores ($z = 1.706$, SE = 0.438, $p = 0.088$), such that subjects showed more improvement in the second phase of the study, regardless of whether or not they were on placebo or fluoxetine.

Treatment Emergent Adverse Effects

Side effects, as measured by side effects symptom checklist, and which include any subject who endorsed a checklist symptom at any time during either condition (drug or placebo), did not significantly or marginally differ between liquid fluoxetine and placebo (Table 3). Patients treated with liquid fluoxetine were numerically less likely to report insomnia: 35.9% (10 mild, four, moderate, 0 severe) *vs* 47.2% (13 mild, four moderate, 0 severe), anxiety: 15.4% (six mild, 0 moderate, 0 severe) *vs* 33.3% (11 mild, one moderate, 0 severe), and urinary incontinence 10.3% (four mild, 0 moderate, 0 severe) *vs* 19.4% (seven mild, 0 moderate, 0 severe) and more likely to report sedation: 17.9% (five mild, two moderate, 0 severe) *vs* 11.1% (three mild, one moderate, 0 severe), agitation: 46.2% (12 mild, six moderate, 0 severe) *vs* 44.4% (13 mild, three moderate, 0 severe), diarrhea: 5.4% (two mild, 0 moderate, 0 severe) *vs* 19.4% (seven mild, 0 moderate, 0 severe) and anorexia: 15.4% (six mild, 0 moderate, 0 severe) *vs* 11.1% (four mild, 0 moderate, 0 severe). One subject reported mild weight gain while on placebo, while no subjects reported weight gain on fluoxetine. Thus, the frequency and severity of side effects did not differ in the drug *vs* placebo condition. In addition, there was no trend or significant effect of drug *vs*

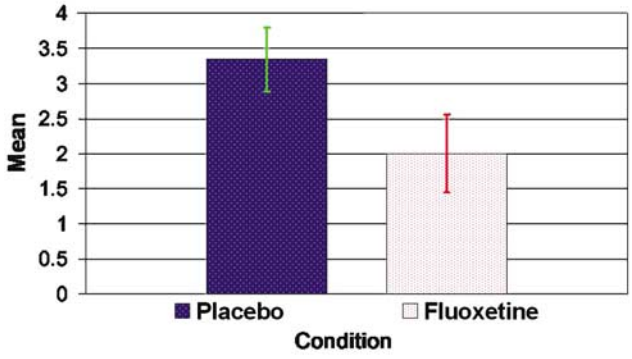

Figure 3 Effect of fluoxetine/placebo on global composite improvement measure (CGI-global autism composite improvement). Fluoxetine was marginally superior to placebo on the improvement of the augmented autism change scores ($z = -1.907$, SE = 0.703, $p = 0.056$).

Table 3 Symptoms Endorsed on Side Effects Checklist

Symptom	Fluoxetine	Placebo
Anxiety/nervousness	15.9% (6/39)	33.3% (12/36)
Insomnia	35.9% (14/39)	47.2% (17/36)
Drowsiness/fatigue/sedation	17.9% (7/39)	11.1% (4/36)
Agitation	46.2% (18/39)	44.4% (16/36)
Diarrhea	5.1% (2/39)	19.4% (7/36)
Anorexia	15.4% (6/39)	11.1% (4/36)
URI	10.3% (4/39)	19.4% (7/36)
Weight gain	0% (0/39)	2.8% (1/36)

placebo on the suicide subscale of the OAS-M. In fact, only one subject had suicidal ideation at any point during the trial, and this occurred in this subject's first phase and on placebo. Six out of 37 subjects (16%) had a dosage reduction due to agitation while on fluoxetine, while two out of 36 (5%) had a dosage reduction due to agitation while on placebo, and one subject was reduced due to activation in both phases, for a total of nine subjects who had dosage reduced due to activation while on placebo or fluoxetine. Thus, the proportion of subjects having dosage reduction on the two treatment due to AEs was not statistically significant ($p = 0.289$, McNemar's test for dependent proportions).

DISCUSSION

This study is the first double-blind, placebo-controlled crossover study of the effects of liquid fluoxetine in children and adolescents with autism. This represents an important contribution to the literature because while fluoxetine is frequently prescribed for children and adolescents with autism, to date no controlled data exist regarding its safety and efficacy. We chose to focus on repetitive behaviors in this study because we believed they would be the target symptom most affected by treatment with fluoxetine of the three core features of ASD. We found that liquid fluoxetine was superior to placebo in reducing repetitive behaviors on the CY-BOCS outcome measure. There was a significant drug by time effect, with a medium to large effect size (0.76).

We were also interested in whether or not global measures of ASD would show improvement with fluoxetine. Using the CGI-AD, which focused on global severity independent of our target behavior, we did not find a significant effect in reducing global autism severity. However, the emphasis we placed in our CGI-AD measure was on the social and communication domains, which are less likely to show improvement over an 8-week period, than our core target symptom of repetitive behaviors. Further, the crossover study design introduced a phase order effect that adversely influenced the CGI-AD, with subjects in both groups showing more improvement in the second phase. This phase order effect may have been due, in part, to the fact that the 4-week washout phase allowed only for 1.75 half-lives of the metabolite. In contrast, our global autism composite improvement score weights changes in observable behaviors as measured by the CY-BOCS and may be a more appropriate outcome measure for a short-term trial, and this composite global measure did not have a phase order effect. The composite measure more closely parallels the way the CGI-AD measure has been used in other trials (Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2002) where the focus was on global behavior, rather than core features of autism such as language and social reciprocity.

Our results demonstrate that liquid fluoxetine reduced repetitive behaviors in children and adolescents with autism. We found a statistically significant reduction in repetitive behaviors, with a moderate to large effect size (0.76). However, the effects of fluoxetine on global autism symptoms did not reach statistical significance. Nevertheless, our global composite measure did approach statistical significance for fluoxetine ($p = 0.056$), and 19 out of 34 subjects (56%) showed a global composite improvement score of 2 (much improved) or better on fluoxetine. This suggests that the effect may be clinically meaningful. However, prior findings in adults with autism with fluvoxamine (McDougle *et al*, 1996b) and clomipramine (Gordon *et al*, 1993) were even more robust, showing statistical separation in parallel design studies of similar sample size, whereas our study did not reach statistical significance in a *post hoc* comparison of the first phase only. Since this study was conducted with children and adolescents, dosing levels were kept low, and were thus much lower than doses typically used in adult trials. This difference in dosing could account for the more robust findings in adults with autism in response to SSRIs. Another possible explanation is that subjects in the adult trials had greater severity of repetitive behaviors at baseline, and thus had the possibility of a greater reduction over time.

The decision to use any medication in autism must balance the benefits *vs* risks to the patient (Hollander *et al*, 2003b). The use of clomipramine in children with autism is complicated because of potential side effects of sedation, weight gain, lowering of the seizure threshold, and cardiac conduction delay, which could result in sudden death. We found no differences in side effects while on fluoxetine and placebo. Further, in contrast to findings with atypicals such as risperidone, there was no reported gain in weight on fluoxetine. Of particular interest, there was no increase in the suicide subscale on the OAS-M, and numerically less anxiety/nervousness on fluoxetine than placebo. This is important, given the recent concern regarding SSRIs and suicidal symptoms in childhood depression in Great Britain (Ramchandani, 2004). Agitation specifically as an adverse event was hard to assess in this study because it was not rated at baseline, so that reported adverse events may or may not be treatment emergent and could be a continuation of baseline symptoms. Overall, we did not detect significant differences in side effects between placebo and our low doses and slow titration of fluoxetine.

This study is limited in several respects. The two-phase 8-week acute trial limits our understanding to the short-term effects of liquid fluoxetine in autism. Longer-term maintenance trials are still necessary to assess long-term efficacy and side effects. The crossover design of this study, while allowing for within-subject comparison, also allowed for phase order effects, which may have partially obscured differences on the global autism measure. This study also used relatively low doses, and may not generalize to effects on higher doses. In addition, our understanding of the use of fluoxetine is limited to noninstitutionalized outpatients and only children 5-years and older. Future studies should focus on institutionalized and noninstitutionalized patients, as well as younger children, since SSRIs may promote neurogenesis (Gaspar *et al*, 2003) and differentiation factors in early brain development. This study focused on repetitive behaviors; future studies should assess in a more specific manner possible improvements in the other core deficits in social and communication function.

Issues of polypharmacy need to be addressed with future studies; in general, the approach taken in treating autism has been to prescribe medications for symptoms, since no medication has proven to be effective in reducing overall

core symptoms, and to balance the risk/benefit ratio for any individual patient. Some medications may be effective in reducing several problem behaviors, such as risperidone, which was shown to be effective for repetitive behaviors as well as disruptive behaviors in a controlled study (Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2002). While antipsychotics such as risperidone may have adverse effects not found with fluoxetine, a risk/benefit ratio assessment would also have to consider that they are effective in reducing a broader range of symptoms. Ideally, medications that improve multiple domains may be used for patients presenting with multiple problems, but must be balanced against potential side effects. Whether or not to prescribe multiple medications should be subject to a careful risk/benefit analysis for any individual patient.

Since autism is a heterogeneous disorder, with different subtypes and profiles, future studies with larger samples sizes are also needed in order to stratify the population into subgroups based on target symptoms, as well as other factors such as genotypes of various 5HT polymorphisms, to determine their association with treatment response and side effects. Nevertheless, these findings are important to the field and serve as a guide to effects of SSRIs in this disabling disorder.

ACKNOWLEDGEMENTS

This work was supported by Orphan Products Division of the Food and Drug Administration Grant # FD-R-001520-01-03, NIH STAART Center of Excellence Grant #1U54 MM066673-01A1, NARSAD Young Investigator Award for Dr Novotny, and the Seaver Foundation. Lilly Research Laboratories provided liquid fluoxetine and matching placebo for the study. We acknowledge Charles Cartwright MD, Katherine Delaney PhD, and Sallie Jo Hadley MD for their clinical contributions to this study.

REFERENCES

Chugani DC, Muzik O, Rothermel R, Behen M, Chakraborty P, Magner T *et al* (1997). Altered serotonin synthesis in the dentathalmocortical pathway in autistic boys. *Ann Neurol* **42**: 666–669.

Cook EH, Leventhal BL (1996). The serotonin system in autism. *Curr Opin Pediatr* **8**: 348–354.

DeLong GR, Ritch CR, Burch S (2002). Fluoxetine response in children with autistic spectrum disorders: correlation with familial major affective disorder and intellectual achievement. *Dev Med Child Neurol* **44**: 652–659.

Fatemi SH, Realmuto GM, Khan L, Thuras P (1998). Fluoxetine in treatment of adolescent patients with autism: a longitudinal open trial. *J Autism Dev Disord* **28**: 303–307.

Gaspar P, Cases O, Maroteaux L (2003). The developmental role of serotonin: news from mouse molecular genetics. *Nat Rev Neurosci* **4**: 1002–1012.

Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischman RL, Hill CL *et al* (1989). The Yale-brown obsessive compulsive scale I. Development, use, and reliability. *Arch Gen Psychiatry* **4**: 1006–1011.

Gordon CT, State RC, Nelson JE, Hamburger SD, Rapoport JL (1993). A double-blind comparison of clomiprmine, despramine, and placebo in the treatment of autistic disorder. *Arch Gen Psychiatry* **50**: 441–447.

Greist J, Chouinard G, DuBoff E, Halaris A, Kim SW, Koran L *et al* (1995). Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. *Arch Gen Psychiatry* **52**: 289–295.

Guy W (1976). *ECDEU Assessment Manual for Psychopharmacology*, NIMH Publication DHEW Publ No. 76-388. National Institute of Mental Health: Bethesda, MD.

Hedeker D, Gibbons RD (1996). MIXREG: a computer program for mixed effects regression analysis with autocorrelated errors. *Comput Methods Programs Biomed* **49**: 229–252.

Hollander E, Koran LM, Goodman WK, Greist JH, Ninan PT, Yang H *et al* (2003a). A double blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. *J Clin Psychiatry* **64**: 640–647.

Hollander E, Novotny S, Allen A, Aronowitz B, Cartwright C, DeCaria C (2000). The relationship between repetitive behaviors and growth hormone response to sumatriptan challenge in adult autistic disorder. *Neuropsychopharmacology* **22**: 163–167.

Hollander E, Phillips AT, Yeh C (2003b). Targeted treatments for symptom domains in child and adolescent autism. *Lancet* **362**: 732–734.

Markowitz PI (1992). Effect of fluoxetine on self-injurious behavior in the developmentally disabled: a preliminary study. *J Clin Psychopharmacol* **12**: 27–31.

McDougle CJ, Kresch LE, Posey DJ (2000). Repetitive thoughts and behavior in pervasive developmental disorders: treatment with serotonin reuptake inhibitors. *J Autism Dev Disord* **30**: 427–435.

McDougle CJ, Naylor ST, Cohen DJ, Aghajanian GK, Heninger GR, Price LH (1996a). Effects of trytophan depletion in drug-free adults with autistic disorder. *Arch Gen Psychiatry* **53**: 993–1000.

McDougle CJ, Naylor ST, Cohen DJ, Volkmar FR, Heninger GR, Price LH (1996b). A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. *Arch Gen Psychiatry* **53**: 1001–1008.

Namerow LB, Prakash T, Bostic JQ, Prince J, Monuteaux MC (2003). Use of citalopram in pervasive developmental disorders. *J Dev Behav Pediatr* **24**: 104–108.

Novotny S, Hollander E, Allen A, Mosovich S, Aronowitz B, Cartwright C *et al* (2000). Increased growth hormone response to sumatriptan challenge in adult autistic disorders. *Psychiatry Res* **94**: 173–177.

Pascual J, del Arco C, Romon T, del Olmo E, Castro E, Pazos A (1996). Autoradographic distribution of (3H) sumatriptan-binding sites in post-mortem human brain. *Cephalagia* **16**: 317–322.

Ramchandani P (2004). Treatment of major depressive disorder in children and adolescents. *Br Med J* **328**: 3–4.

Research Units on Pediatric Psychopharmacology Autism Network (2002). Risperidone in children with autism and serious behavioral problems. *N Engl J Med* **347**: 314–321.

The Clomipramine Collaborative Study Group (1991). Clomiprmine in the treatment of patients with obsessive-compulsive disorder. *Arch Gen Psychiatry* **48**: 730–738.

Tollefson GD, Rampey Jr AH, Potvin JH, Jenike MA, Rush AJ, Kominguez RA *et al* (1994). A multicenter investigation of fixed dose fluoxetine in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry* **51**: 559–567.