Pharmacotherapy in Autism: Time for an Update

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UW Medicine SCHOOL OF MEDICINE | Seattle Children's HOSPITAL • RESEARCH • FOUNDATION

Lewis MA, Lewis C, Leake B, King BH, Lindeman R.
Public health issues: The quality of health care for adults with developmental disabilities. *Public Health Reports*, 117:174-184, 2002.

33% were receiving at least one psychotropic medication (antipsychotics, antidepressants, anticholinergics (artane, cogentin), lithium, stimulants, and anxiolytics).

Only 24% of those medicated had evidence of a psychiatric consultation in their record.

25% of persons on antipsychotic drugs had no identifiable psychiatric diagnosis in their records.

80 of the 92 subjects (87%) receiving an anticonvulsant medication had an identifiable diagnosis of a seizure disorder.

Gut 2003;52:1535–1536

Aspirin: still learning about the wonder drug

E T Hawk, J L Viner

Aspirin, taken daily over at least one year, may exert chemopreventive effects against the early stages of colorectal carcinogenesis

Preclinical, observational, and clinical data consistently show that non-steroidal anti-inflammatory drugs (NSAIDs)—particularly aspirin—reduce colorectal carcinogenesis.[1] Scores of animal studies show that NSAIDs inhibit the development of colorectal neoplasia across the spectrum of disease, ranging from aberrant crypt foci humans.[7] ACF—or at least a subset of them—may represent important risk markers for adenoma-carcinoma development in humans. They may also serve as markers of chemopreventive response. Thus although relatively little is known about ACF and their relevance to more advanced stages of colorectal neoplasia in humans, they provide an

RESPONSE TO THORAZINE (CHLORPROMAZINE) ADMINISTRATION IN HYPERKINETIC MONGOLISM

by

HAL W. GEYER, M.D.*

It has been found, following a year of intensive study of hyperkinesia in mentally retarded children afflicted with mongolism, that Thorazine (Chlorpromazine) has been most effective, and the results are equally gratifying.

The purpose of this case report, which is one of the few treated for hyperkinesia, is to not only open a field from the standpoint of treatment in a Hospital for the Mentally Retarded, but for the general practitioner and psychiatrist in private practice, who may be confronted with similar cases.

TRANQUILLIZERS IN MENTAL DEFICIENCY: CHLORPROMAZINE

By M. CRAFT

Royal Western Counties Institution, Starcross, Devon

THE PROBLEM

FEW papers have as yet appeared assessing the effect of tranquillizers upon low-grade defectives. This group of patients constitutes a problem in nursing care by virtue of their destructiveness, aggression, noise and dirty habits. Those tranquillizing drugs such as chlorpromazine reported to reduce psychomotor activity should be eminently suited to hyperactive idiots. The author had previously observed that chlorpromazine aided patients during outbursts and it was decided to evaluate this improvement by use of a rating scale over a longer period. The help of a statistician was sought when the trial was set up.

Table 1

Summary of rating scale

Points removed from acceptable behaviour	*Aggression*	*Activity*	*Social behaviour*
6	Actual injury to others.	Violent, destructive.	Spitting and shouting.
4	Hitting others.	Throwing things.	Resistive.
0	Normal	Reasonable activity.	Responsive.
4	Hurting self.	Sleeping unduly.	Smearing excreta.
6	Actual injury to self.	Stuporose.	Eating excreta.

Craft, 1957

THIORIDAZINE (MELLARIL)

A PSYCHO-SEDATIVE VIRTUALLY FREE OF SIDE-EFFECTS

L. J. LeVANN, L.R.C.P. Edin., L.R.C.S. Edin., L.R.F.P. & S. Glasg.
Medical Superintendent, Provincial Training School, Red Deer, Alberta.
Lecturer in Psychiatry, University of Alberta

Within recent years a wide variety of drugs have appeared which are derivatives of phenothiazine, such as promazine, chlorpromazine, etc. Many of these have shown their undoubted value as 'psycho-inhibitors', or 'psycho-sedatives' in relation to the widest variety of psychoneuroses and psychoses.

To the mental hospitals and residential schools for retarded children, these drugs have revolutionized psychiatric care by the realization of the 'open door' policy and also by diminishing the need for the more hazardous type of physical therapies such as electro-shock and insulin-shock.

These drugs have indirectly made available more mental hospital beds by shortening patient-day stay in hospital and in many cases enabling earlier discharge of patients. They did not, in any way, diminish the contribution to the patient care made by medical or nursing staff, but they rendered the patient more accessible to his therapist and nursing attendants.

Conclusions and Summary:

(1) Thioridazine (Mellaril) was investigated in a group of 97 institutionalized children, comprising retarded as well as emotionally disturbed cases with adequate intelligence.

(2) Thioridazine may be given within an extensive dosage range (10 mg. t. i. d. to 200 mg. q. i. d.) for the control of a wide variety of abnormal behavioural or thinking patterns in children.

(3) No side-effects were observed in the entire study.

(4) Maintenance treatment of out-patients is feasible. Due to the lack of side-effects, it is also safe and carries more assurance that the patient will continue his medication.

(5) This study would rate thioridazine as one of the better ataractics now available.

MENTAL RETARDATION Vol. 34, No. 6, 359–366, December 1996

Substituting Traditional Antipsychotics With Risperidone for Individuals With Mental Retardation

Elliott W. Simon, Kerry M. Blubaugh, and Michael Pippidis

Abstract: The use of risperidone for 10 individuals with mental retardation and mental health disturbances was reported. A case study approach was employed to delineate the course of substitution of more traditional antipsychotic medications with risperidone. At the conclusion of the study, 6 of the 10 individuals had completed the substitution protocol. All participants evidenced improvement or resolution in side effects attributed to previous antipsychotic medication, with no worsening in psychiatric or behavioral status.

National Trends in the Outpatient Treatment of Children and Adolescents With Antipsychotic Drugs

Mark Olfson, MD, MPH; Carlos Blanco, MD, PhD; Linxu Liu, PhD; Carmen Moreno, MD; Gonzalo Laje, MD

Context: Although there are indications that antipsychotic drugs are increasingly used to treat children and adolescents, little is known about the characteristics of those who receive them.

Objective: To examine national trends and patterns in antipsychotic treatment of youth seen by physicians in office-based medical practice.

Design: Analysis of national trends of visits (1993-2002) that included prescription of antipsychotics, and comparison of the clinical and demographic characteristics of visits (2000-2002) that included or did not include antipsychotic treatment.

Setting: Outpatient visits to physicians in office-based practice.

Participants: Patient visits by persons 20 years and younger from the National Ambulatory Medical Care Surveys from 1993 to 2002.

Main Outcome Measures: Visits that included prescription of antipsychotics.

Results: In the United States, the estimated number of office-based visits by youth that included antipsychotic treatment increased from approximately 201 000 in 1993 to 1 224 000 in 2002. From 2000 to 2002, the number of visits that included antipsychotic treatment was significantly higher for male youth (1913 visits per 100 000 population) than for female youth (739 visits per 100 000 population), and for white non-Hispanic youth (1515 visits per 100 000 population) than for youth of other racial or ethnic groups (426 visits per 100 000 population). Overall, 9.2% of mental health visits and 18.3% of visits to psychiatrists included antipsychotic treatment. From 2000 to 2002, 92.3% of visits with prescription of an antipsychotic included a second-generation medication. Mental health visits with prescription of an antipsychotic included patients with diagnoses of disruptive behavior disorders (37.8%), mood disorders (31.8%), pervasive developmental disorders or mental retardation (17.3%), and psychotic disorders (14.2%).

Conclusions: There has been a sharp national increase in antipsychotic treatment among children and adolescents in office-based medical practice. Second-generation antipsychotics are being widely prescribed, and emerging empirical evidence provides a base of support that is limited to short-term safety and efficacy.

Arch Gen Psychiatry. 2006;63:679-685

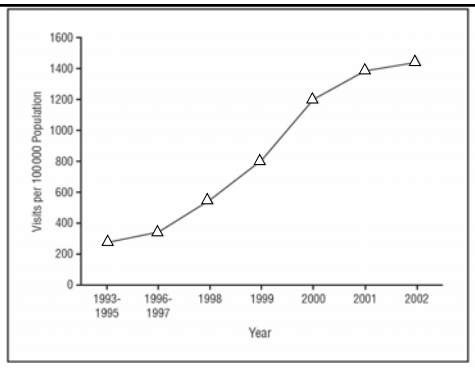

Figure. National trends in office-based visits by children and adolescents that included antipsychotic treatment, 1993-2002. Annualized visit rates per 100 000 population aged 0 to 20 years were calculated using National Ambulatory Medical Care Survey and US Census Bureau data.

Table 2. Demographic and Clinical Characteristics of Office-Based Physician Visits by Children and Adolescents, 2000-2002*

Characteristic	Visits With Antipsychotic Treatment (n = 173)	Visits Without Antipsychotic Treatment (n = 1251)	χ^2 Statistic	*P* Value
Female sex	47 (21.8)	500 (40.6)	9.9	<.001
White non-Hispanic race or ethnicity	120 (85.8)†	873 (82.0)‡	1.0	.32
Health insurance			10.1§	.01
Private	65 (35.9)	693 (59.3)		
Public	64 (38.1)	254 (20.4)		
Other	44 (26.0)	304 (20.3)		
Included psychotherapy	57 (38.8)	356 (25.4)	2.4	.12
Mental disorder diagnosis				
Psychotic disorder	27 (14.2)‖	27 (1.6)‖	8.5	<.001
Disruptive behavior disorder	70 (37.8)	647 (52.1)	3.0	.08
Mood disorder	48 (31.8)	255 (20.7)	3.4	.07
Tic disorder	9 (3.3)‖	25 (0.9)‖	2.1	.15
Pervasive developmental disorder or mental retardation	28 (17.3)‖	53 (3.7)	3.2	.08
Other mental disorder	68 (32.1)	387 (28.3)	0.8	.38
Mental disorder comorbidity present	86 (44.6)	343 (21.2)	9.6	<.001
Other psychotropic medications				
Stimulants	66 (44.2)	508 (39.9)	0.4	.55
Antidepressants	67 (33.7)	394 (27.9)	2.1	.15
Anxiolytics and hypnotics	18 (9.7)‖	70 (4.9)	2.9	.09
Mood stabilizers	63 (37.2)	106 (5.9)	12.0	<.001
Treatment by psychiatrist	161 (89.5)	724 (40.3)	27.5	<.001
Age, mean ± SE, y	12.8 ± 0.6	12.1 ± 0.2	1.4¶	.17
Visit duration, mean ± SE, min	27.0 ± 2.3	25.6 ± 0.9	0.7¶	.48

*Data are given as weighted visits (percentage) unless otherwise indicated and are calculated using National Ambulatory Medical Care Survey and US Census Bureau data for persons aged 0 to 20 years with a mental health visit (mental disorder diagnosis, visit to a psychiatrist, or provision of psychotherapy).
†Race or ethnicity is missing for 23 of 173 mental health visits with antipsychotic treatment.
‡Missing for 192 visits.
§2 df.
‖Unreliable estimate based on fewer than 30 visits.
¶*t* Test.

Table 3. Predictors of Office-Based Physician Visits by Children and Adolescents That Included Antipsychotic Treatment, 2000-2002*

Predictor	Odds Ratio (95% Confidence Interval)	Logistic Regression Analysis†
Mental disorder diagnosis vs none		
Psychotic disorder	25.9 (7.9-85.1)	$t = 5.4$, $P < .001$
Disruptive behavior disorder	0.5 (0.3-1.0)	$t = -2.1$ $P = .03$
Mood disorder	2.9 (1.2-7.0)	$t = 2.4$, $P = .02$
Tic disorder	7.2 (1.9-28.1)	$t = 2.9$, $P < .001$
Pervasive developmental disorder or mental retardation	5.8 (2.4-13.9)	$t = 4.0$, $P < .001$
Other mental disorder	1.3 (0.7-2.5)	$t = 0.9$, $P = .38$
Mental disorder comorbidity present vs absent	1.1 (0.5-2.2)	$t = 0.2$, $P = .81$

In recent years, second-generation antipsychotic medications have become common in the office-based mental health treatment of young people. These medications are used to treat children and adolescents with different mental disorders. Results of clinical trials provide a limited base of support for the short-term safety and efficacy of some second-generation antipsychotic medications for psychosis and disruptive behavior disorders. In light of the widespread and growing use of these medications, there is a pressing need to increase and extend the experimental evaluation of these medications in children and adolescents.

Table I. Number of Subjects Taking Agents on Date of the Survey

et al., JADD, 2

• Drug type	Number	Percentage
Anticonvulsants	48	12
Antipsychotics	62	15
Antidepressants	90	22
Mood Stabilizers	19	5
Stimulants	47	11
Sedatives or hypnotics	36	9
Antihypertensives	52	13
Opiate Blockers	0	0
Vitamins (for autism)	43	10

Psychotropic drugs	N	%
One drug	103	25
Two drugs	41	10
Three drugs	32	8
Four drugs	10	2
Five drugs	3	1
Eight drugs	1	.2
Total	190	45.6

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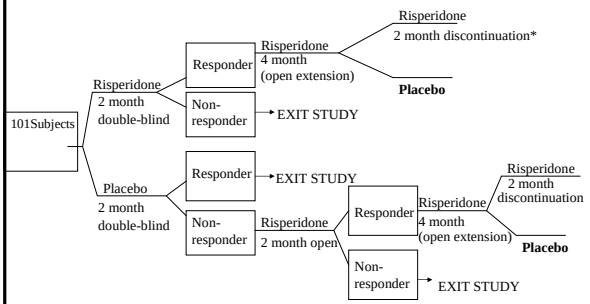
Medication Use Among Children with Autism-Spectrum Disorders

The study characteriz… autism-spectrum diso… ple had at least one … therapeutic classes. Th… antidepressants, stim… agents, anxiolytic/sed… noses indicate that chi… spectrum diagnosis, ev… mental disorders. Age… ders age 8 yr and up receive some form of psychoactive medication in a given year.

TABLE 2. MOST COMMON THERAPEUTIC CLASSES OF DRUGS

Therapeutic class	*Number of individuals*
Antidepressants	768
Stimulants	641
Tranquilizers/antipsychotics	561
Anticonvulsants, miscellaneous	343
Hypotensive agents	285
Anxiolytic/sedative/hypnotic	139
Benzodiazepines	100

Acute Risperidone Trial: RUPP

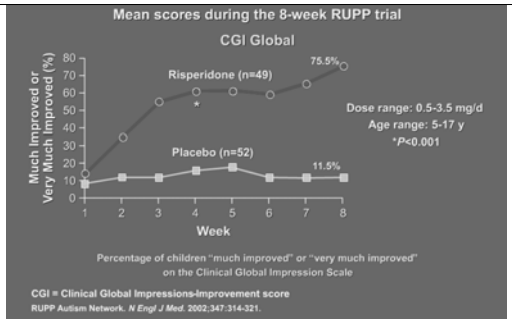


Acute Risperidone Trial: RUPP in Children and Adolescents

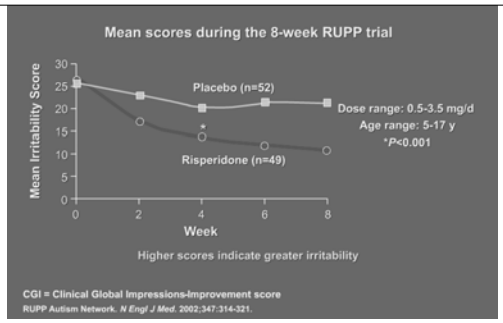
- 101 subjects (82 boys, 19 girls)
- Diagnosis = autistic disorder, ADI-R
- 8 week, double-blind, parallel groups
- Mean age = 8.8 ± 2.7 y; range = 5-17 y
- Risperidone 1.8 mg/d; range = 0.5-3.5 mg/d

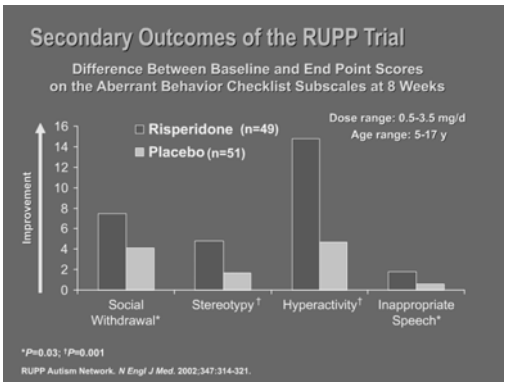
ADI-R = Autism Diagnostic Interview–Revised.
RUPP Autism Network. *N Engl J Med.* 2002;347:314-321.

Risperidone



Risperidone





The New England Journal of Medicine

RISPERIDONE IN CHILDREN WITH AUTISM AND SERIOUS BEHAVIORAL PROBLEMS

RESEARCH UNITS ON PEDIATRIC PSYCHOPHARMACOLOGY AUTISM NETWORK*

Conclusions Risperidone was effective and well tolerated for the treatment of tantrums, aggression, or self-injurious behavior in children with autistic disorder. The short period of this trial limits inferences about adverse effects such as tardive dyskinesia. (N Engl J Med 2002;347:314-21.)

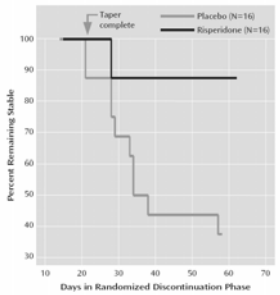
Acute Risperidone Trial: RUPP (Adverse effects)

- Mean increase in weight
  - Risperidone, 2.7 ± 2.9 kg
  - Placebo, 0.8 ± 2.2 kg, $P = 0.001$
- Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group; all $P < 0.05$
- AIMS and Simpson-Angus: no EPS

RUPP Autism Network. *N Engl J Med.* 2002;347:314-321.

RUPP AUTISM NETWORK

FIGURE 2. Survival Analysis for Children With Autism Who Responded to Risperidone and Were Then Randomly Assigned to Placebo or Continued Risperidone for 8 Weeks[a]



[a] For the placebo group, the risperidone dose was decreased by 25% per week. Relapse was defined as a 25% increase in the score on the Aberrant Behavior Checklist irritability subscale and a CGI improvement rating of much worse or very much worse, compared to the prediscontinuation baseline, for at least 2 consecutive weeks. The difference between groups was significant (test for equality of survival distributions for treatment, log rank=6.89, df=1, p=0.009).

FDA indication

RISPERDAL (risperidone), for the treatment of irritability associated with autistic disorder, including symptoms of aggression, deliberate self-injury, temper tantrums and quickly changing moods, in children and adolescents aged five to 16 years.

ABC Irritability Subscale Items

2. Injures self on purpose
4. Aggressive to others (verbal or physical)
8. Screams inappropriately
10. Temper tantrums/outbursts
14. Irritable and whiny
19. Yells at inappropriate times
25. Depressed mood
29. Demands must be met immediately
34. Cries over minor annoyances/hurts
36. Mood changes quickly
41. Cries and screams inappropriately
47. Stamps feet or bangs objects/slams doors
50. Deliberately hurts self
52. Does physical violence to self
57. Has temper outbursts/tantrums when does not get own way.

ORIGINAL ARTICLE

Randomized, Controlled, Crossover Trial of Methylphenidate in Pervasive Developmental Disorders With Hyperactivity

Research Units on Pediatric Psychopharmacology (RUPP) Autism Network

Arch Gen Psychiatry. 2005;62:1266-1274

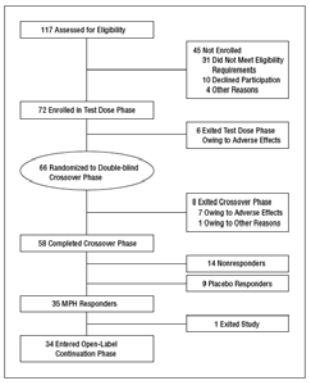


Figure 1. Diagram of subject screening, enrollment, and flow through all of the phases of methylphenidate hydrochloride (MPH) treatment.

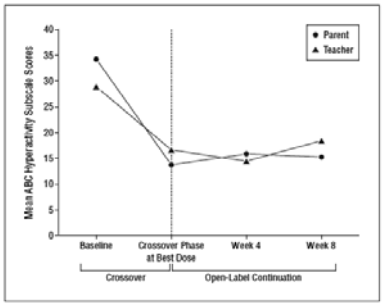
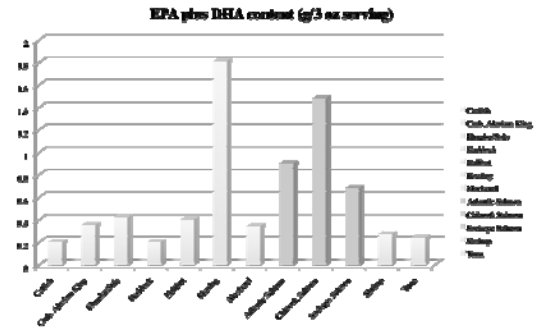


Figure 2. Mean Aberrant Behavior Checklist (ABC) hyperactivity subscale scores as rated by teachers and parents at baseline, at the best dose of methylphenidate during the crossover phase, and during the methylphenidate hydrochloride open-label continuation phase. Linear slopes were used to examine the change in the primary outcome measure over time during the 8-week open-label continuation phase. Parent-rated ($F=1.09$; $P=.30$) and teacher-rated ($F=3.01$; $P=.10$) ABC hyperactivity subscale score slopes were not significantly different from 0, suggesting a maintenance of response.

Results: Methylphenidate was superior to placebo on the primary outcome measure, with effect sizes ranging from 0.20 to 0.54 depending on dose and rater. Thirty-five (49%) of 72 enrolled subjects were classified as methylphenidate responders. Adverse effects led to the discontinuation of study medication in 13 (18%) of 72 subjects.

Clinical Trials

Intervention	Age	Studies (No.)	Intervention	Age	Studies (No.)
Galantamine	Child	1	Hyperbaric O2	Child/Adult	8
Donepezil	Child	2	Divalproex	Child/Adult	3
Minocycline	Child	2	Secretin	Child	3
DMSA (chel)	Child	1	Oxcarbazepine	Child	1
Atomoxetine	Child	5	Oxytocin	Adult	2
CM-AT	Child	1	Fluvoxamine	Child	1
Oralglam (IG)	Child	1	Sertraline	Child	1
Mecamylamine	Child	1	CX516 (ampalex)	Adult	1
Mercury Chel	Child	1	STX209(rBaclofen)	Child	1
Fluoxetine	Child/Adult	6	Omega 3 FA	Child	2
Memantine	Child	1	Ziprasidone	Child	1
D-Cycloserine	Child	2	Aripiprazole	Child/Adult	10
Buspirone	Toddler	2	Methyl B12	Child	2
N-acetycysteine	Child	3	Paliperone ER	Child/Adult	1



Adapted from Covington, M. Omega 3 Fatty Acids. Am Fam Physician 2004;70:133- 40.

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DISTRIBUTION OF ACIDIC AND NEUTRAL DRUGS IN SURFACE WATERS NEAR SEWAGE TREATMENT PLANTS IN THE LOWER GREAT LAKES, CANADA

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‡Environment Canada, Burlington, Ontario L7R 4A6

(*Received* 18 *December* 2002; *Accepted* 13 *May* 2003)

Abstract—Prescription and nonprescription drugs have been detected in rivers and streams in Europe and the United States. Sewage treatment plants (STPs) are an important source of these contaminants, but few data exist on the spatial distribution of drugs in surface waters near STPs. Samples of surface water were collected in the summer and fall of 2000 at open-water sites in the lower Great Lakes (Lake Ontario and Lake Erie), at sites near the two STPs for the city of Windsor (ON, Canada), and at sites in Hamilton Harbour (ON, Canada), an embayment of western Lake Ontario that receives discharges from several STPs. In a follow-up study in the summer of 2002, samples of surface water and final effluent from adjacent STPs were collected from sites in Hamilton Harbour and Windsor. In addition, surface water and STP effluent samples were collected in Peterborough (ON, Canada). All samples of surface water and STP effluents were analyzed for selected acidic and neutral drugs. In the survey of Hamilton Harbour and Windsor conducted in 2000, acidic drugs and the antiepileptic drug carbamazepine were detected at ng/L concentrations at sites that were up to 500 m away from the STP, but the hydrological conditions of the receiving waters strongly influenced the spatial distribution of these compounds. Drugs were not detected at open-water locations in western Lake Erie or in the Niagara River near the municipality of Niagara-on-the-Lake (ON, Canada). However, clofibric acid, ketoprofen, fenoprofen, and carbamazepine were detected in samples collected in the summer of 2000 at sites in Lake Ontario and at a site in the Niagara River (Fort Erie, ON, Canada) that were relatively remote from STP discharges. Follow-up studies in the summer of 2002 indicated that concentrations of acidic and neutral drugs in surface waters near the point of sewage discharge into the Little River (ON, Canada) STP were approximately equal to the concentrations in the final effluent from the STP. Caffeine and cotinine, a metabolite of nicotine, were generally present in STP effluents and surface waters contaminated by drugs. The antidepressant fluoxetine and the antibiotic trimethoprom were also detected in most STP effluents and some surface water samples. For the first time, the lipid regulating drug atorvastatin was detected in samples of STP effluent and surface water.

Keywords—Pharmaceuticals Sewage Carbamazepine Fluoxetine Atorvastatin

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Medication Use Among Children with Autism-Spectrum Disorders

Donald P. Oswald, Ph.D., and Neil A. Sonenklar, M.D.

Age data indicate that about 70% of children with autism-spectrum disorders age 8 yr and up receive some form of psychoactive medication in a given year

antidepressants, stimulants, tranquilizers/antipsychotics, anticonvulsants, hypotensive agents, anxiolytic/sedative/hypnotics, and benzodiazepines. The data on other relevant diagnoses indicate that children and youth are frequently treated with medication under an autism-spectrum diagnosis, even though the target symptoms may be commonly associated with other mental disorders. Age data indicate that about 70% of children with autism-spectrum disorders age 8 yr and up receive some form of psychoactive medication in a given year.

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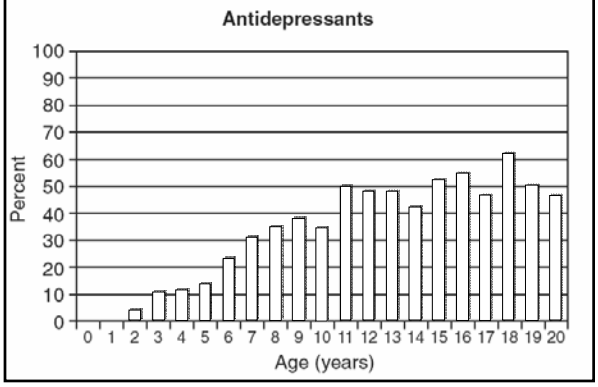

SSRIs in ASD

- Although no medications are FDA-approved for core symptoms of ASD, medication use in this population is common.
- The global market for autism therapeutics is presently estimated at between $2.2 billion and $3.5 billion.
- Selective serotonin reuptake inhibitors (SSRIs) account for the greatest global market share (59%) reflecting the combination of cost and frequency of prescription.

- Repetitive behaviors 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 similarities between repetitive behaviors in ASD and obsessive-compulsive disorder (OCD), and findings of serotonin system abnormalities in autism, anti-obsessional agents such as the SSRIs have been of interest.

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

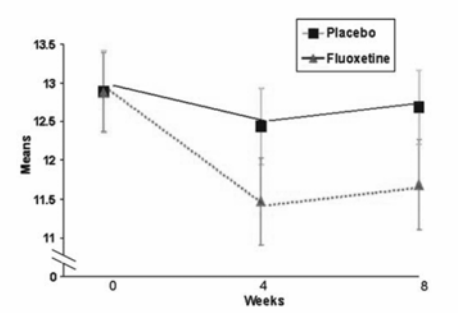

Figure 1 Effect of fluoxetine/placebo on repetitive behaviors (CY-BOCS Compulsion Score). Fluoxetine was superior to placebo on mean CY-BOCS with a linear trend by treatment interaction ($z = -2.075$, SE = 0.407, $p = 0.038$), as well as significant direct effects for treatment ($z = -2.852$, SE = 0.246,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

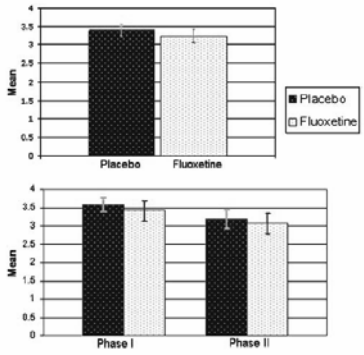

Figure 2 Effects of phase order and treatment condition on global CGI-AD improvement. There was an interaction of condition and treatment on the Global CGI-AD scores ($z = 1.706$, SE = 0.438, $p = 0.088$), such that subjects showed more improvement in the second phase of the study, regardless of whether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

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Use of Citalopram in Pervasive Developmental Disorders

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ABSTRACT. This study assessed the effectiveness and tolerability of the selective serotonin reuptake inhibitor citalopram in the treatment of patients with pervasive developmental disorders (PDDs). The medical charts of 15 children and adolescents (aged 6–16 yr) with Asperger syndrome, autism, or PDD not otherwise specified treated with citalopram were retrospectively reviewed. The final dose of citalopram was 16.9 ± 12.1 mg/day with a treatment duration of 218.8 ± 167.2 days. Independent ratings of the Clinical Global Impression (CGI) Severity and Improvement scales allowed comparison between baseline and PDD symptoms at the last visit. Eleven adolescents (73%) exhibited significant improvement in PDD, anxiety, or mood CGI score ($z = 2.95$; $p = .003$). Anxiety symptoms associated with PDDs improved significantly in 66% of patients ($z = 2.83$, $p = .005$), and mood symptoms improved significantly in 47% of patients ($z = 2.78$, $p = .005$). Mild side effects were reported by five patients (33%). These data suggest citalopram may be effective, safe, and well tolerated as part of the treatment of PDDs. *J Dev Behav Pediatr 24:104–108, 2003.*
Index terms: *citalopram, pediatrics, antidepressants, pervasive developmental disorder, autism.*

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A Retrospective Assessment of Citalopram in Children and Adolescents with Pervasive Developmental Disorders

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ABSTRACT

Although selective serotonin reuptake inhibitors have been used to treat symptoms of aggression and anxiety in children and adolescents with pervasive developmental disorders (PDDs), there are no published reports of the use of citalopram in this population. The purpose of this study was to examine the benefits and adverse effects of citalopram in a group of children and adolescents with PDDs. Target behaviors included aggression, anxiety, stereotypies, and preoccupations. Seventeen patients with PDDs (14 with autistic disorder, three with Asperger's disorder) (mean age = 9.4 ± 2.9 years; range 4–15 years) were treated with citalopram for at least 2 months (mean duration of treatment = 7.4 ± 5.3 months; range 1–15 months). Treatment was initiated at a low dose (5 mg daily) and was increased by 5 mg weekly as tolerated and as necessary. The mean final dose was 19.7 ± 7.8 mg (range 5–40 mg). Outcome was based on a consensus between clinician and parents, using the Improvement item of the Clinical Global Impressions Scale as a guide. Ten (59%) children were judged to be much improved or very much improved regarding target behaviors. Core symptoms of PDDs (social interactions, communication) did not show clinically significant improvement. Citalopram was generally well tolerated, although four patients developed treatment-limiting adverse effects: two with increased agitation, one with insomnia, and one with possible tics. The results of this case series suggest that citalopram has beneficial effects on some interfering behaviors associated with PDDs with few adverse effects. Controlled trials are warranted.

An Open-Label Trial of Escitalopram in Pervasive Developmental Disorders

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ABSTRACT

Objective: To assess the effect of escitalopram in the treatment of pervasive developmental disorders (PDDs). **Method:** This 10-week study had a forced titration, open-label design. Twenty-eight subjects (mean age 125.1 ± 33.5 months) with a PDD received escitalopram at a dose that increased weekly to a maximum dose of 20 mg as tolerated. The Aberrant Behavior Checklist-Community Version (ABC-CV) and the Clinical Global Impression scale (CGI) were used to assess outcome. **Results:** There was significant improvement in ABC-CV Irritability Subscale Scores (baseline mean 20.5 ± 5.9 to final mean 10.9 ± 7.2; $p \leq .001$) and in the other ABC-CV Subscales. Improvement on Clinical Global Improvement Scale severity rating was also significant (baseline mean 5.2 ± 1.0 to final mean 4.6 ± 1.2; $p \leq .001$). Twenty-five percent of the subjects responded at a dose less than 10 mg and did not tolerate the 10-mg dose, and an additional 36% responded at a dose greater than or equal to 10 mg. Final dose was unrelated to weight and only weakly correlated with age. **Conclusions:** This open-label study found escitalopram to be useful in treating some difficulties common in PDDs. A wide variability in dose was found that could not be accounted for by weight and only partially by age. The study provides information useful for the design of double-blind, placebo-controlled studies of escitalopram in PDDs. *J. Am. Acad. Child Adolesc. Psychiatry,* 2005;44(4):343–348. **Key Words:** autistic disorder, escitalopram, drug treatment, open label.

Fluvoxamine

- The SSRI, fluvoxamine, was superior to placebo for repetitive behavior, aggression, and social relatedness in adults with autism.
- However, in a placebo-controlled study of the same medication in children, only one of eighteen subjects demonstrated improvement on active drug. Furthermore, adverse effects including hyperactivity, insomnia, agitation, and aggression occurred in fourteen of eighteen fluvoxamine-treated children, suggesting unusual sensitivity of children with ASD to this SSRI

US Children's Health Act (2000)

- Established coordinated centers of excellence, the Studies to Advance Autism Research and Treatment (STAART) Network, sponsored by several NIH Institutes including NINDS, NIMH, NIDCD, NIEHS and NICHD.

❖Citalopram is available in a liquid formulation allowing for small dose adjustments.

❖Potential advantages for citalopram include relatively greater specificity at the serotonin transporter, reduced drug-drug interactions via the cytochrome p450 isoenzymes, and a favorable half-life compared to other members from this class.

❖Reports from 2 open trials show promising results for citalopram.

Citalopram/repetitive behavior

- **OBJECTIVE**
- To evaluate the efficacy in improving global functioning (utilizing the CGI-I measure), safety and tolerability (including optimal dosing) of citalopram in children and adolescents with autism spectrum disorders with a high level of repetitive behaviors.

Inclusion Criteria

❖5-17 years old;

❖Meet DSM IV-TR criteria for Autistic Disorder, Asperger Disorder, or PDD-NOS as determined by an experienced clinician and informed by the ADI-R and ADOS;

❖Have an illness severity rating at least Moderate on the Clinical Global Impression-Severity scale (CGI-S);

❖Score moderate or higher on compulsive behaviors (≥ 8 on the sum of items 1A, 2, 3 and 5) on the CYBOCS-PDD.

Children's Yale-Brown Obsessive Compulsive Scale Modified for Pervasive Developmental Disorders

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ABSTRACT

Objective: To examine the psychometric properties of the Children's Yale-Brown Obsessive Compulsive Scales (CYBOCS) modified for pervasive developmental disorders (PDDs). **Method:** Raters from five Research Units on Pediatric Psychopharmacology (RUPP) Autism Network were trained to reliability. The modified scale (CYBOCS-PDD), which contains only the five Compulsion severity items (range 0–20), was administered to 172 medication-free children (mean 8.2 ± 2.6 years) with PDD (autistic disorder, $n = 152$; Asperger's disorder, $n = 6$; PDD not otherwise specified, $n = 14$) participating in RUPP clinical trials. Reliability was assessed by intraclass correlation coefficient (ICC) and internal consistency by Cronbach's α coefficient. Correlations with ratings of repetitive behavior and disruptive behavior were examined for validity. **Results:** Eleven raters showed excellent reliability (ICC = 0.97). The mean CYBOCS score was 14.4 (± 3.86) with excellent internal consistency ($\alpha = .85$). Correlations with other measures of repetitive behavior ranged from $r = 0.11$ to $r = 0.28$ and were similar to correlations with measures of irritability ($r = 0.24$) and hyperactivity ($r = 0.25$). Children with higher scores on the CYBOCS-PDD had higher levels of maladaptive behaviors and lower adaptive functioning. **Conclusions:** The five-item CYBOCS-PDD is reliable, distinct from other measures of repetitive behavior, and sensitive to change. *J. Am. Acad. Child Adolesc. Psychiatry.* 2006;45(9):1114–1123. **Key Words:** autism, pervasive developmental disorders, repetitive behavior, clinical measures.

CHILDREN'S YALE-BROWN OBSESSIVE COMPULSIVE SCALE:
Modified for PDD

Primary Informant _____

COMPULSION SCALE

	None	Mild	Moderate	Severe	Extreme
1. TIME SPENT	0	1	2	3	4
1b. COMPULSION-FREE INTERVAL (do not add to total score)	No Symptoms 0	Moderately Long 1	Long 2	Extremely Short 3	Short 4
	None	Mild	Moderate	Severe	Extreme
2. INTERFERENCE	0	1	2	3	4
3. DISTRESS	0	1	2	3	4
	Always resists	Most of the time	Some of the time	Once in awhile	No resistance
4. RESISTANCE	0	1	2	3	4
	Complete control	Much control	Moderate control	Little control	No control
5. CONTROL	0	1	2	3	4

Exclusion Criteria

- ✧Seizure within the past 6 months;
- ✧Medical condition that might interfere with study participation;
- ✧Clinically significant abnormal baseline laboratory tests;
- ✧History of adverse effects or failed treatment on two or more SSRIs;
- ✧Prior treatment with citalopram/escitalopram;
- ✧Recent initiation of behavioral therapy;
- ✧Bipolar disorder or manic episode.

Consolidated Standards for Reporting of Trials (CONSORT) chart

King, B. H. et al. Arch Gen Psychiatry 2009;66:583-590.

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Efficacy Measures:

Primary outcome measure was the Clinical Global Impression-Improvement scale (CGI-I) rated by the evaluating clinician.

The CGI-I is scored from 1– very much improved, to 7 – very much worse. 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.

Inter-rater Reliability

Evaluating clinicians from all sites were trained to reliability on the CYBOCS-PDD, the CGI-S and CGI-I at the beginning and midpoint of the trial.

This training resulted in 95% to 100% percent agreement to within one unit of a gold standard rating.

Demographics and Baseline Characteristics by Treatment Group (ITT Population)

Characteristic	Citalopram (n=73)	Placebo (n=76)
Age (at consent, yrs)		
Mean (Std Deviation)	9.1 (3.2)	9.6 (3.1)
Median	8.6	9
Min-Max	5-17.3	5.1-17.1
Non-verbal IQ > than 70*, n (%)	43 (61.4%)	43 (60.6%)
CGI Severity, n (%)		
4 (Moderately ill)	21 (28.8%)	22 (29.0%)
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, n (%)	64 (87.7%)	64 (84.2%)
Hispanic, n (%)**	9 (12.5%)	8 (10.5%)
Race† , n (%)		
American Indian/Alaskan Native	0 (0%)	2 (2.6%)
Asian	6 (8.2%)	8 (10.5%)
Black	7 (9.6%)	10 (13.2%)
Native Hawaiian	1 (1.4%)	0 (0%)
White	53 (72.6%)	55 (72.4%)
Other	6 (8.2%)	4 (5.3%)
Tanner Stage†† , n (%)		
1	52 (73.2%)	48 (63.2%)
2	10 (14.1%)	12 (15.8%)
≥3	9 (12.7%)	16 (21.1%)

SCAHILL ET AL.

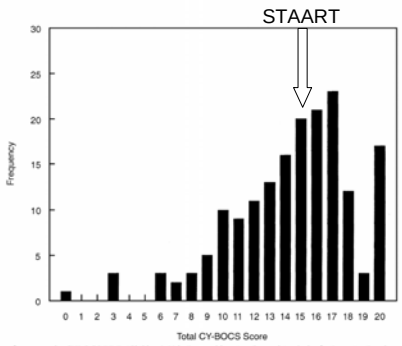

Fig. 1 The distribution of scores on the CYBOCS-PDD (Children's Yale-Brown Obsessive-Compulsive Scales for Pervasive Developmental Disorders) in 172 child participants in RUPP Autism Network trials. The five items are scored from 0 to 4. Higher scores indicate greater system severity; mean score = 14.6 (± 3.86); median = 15; mode = 17; range = 0–20.

CGI Severity Ratings

BASELINE	***STAART***	**RUPP Risp**	**RUPP MPH**
CGI Severity, n (%)	**N=149**	***N=98***	**N=66**
4 (Moderately ill)	**29%**	**18%**	**30%**
5 (Markedly ill)	**50%**	**56%**	**52%**
6 (Severely ill)	**20%**	**24%**	**16%**
7 (Among the most extreme)	**1%**	**1%**	**0**

ABC-CV Ratings

	Citalopram **Baseline**	***Placebo*** **Baseline**	**RUPP** ***Risperidone***	**RUPP** ***MPH***	**Owley et al. escital**
ABC-CV					
Irritability	13.2 (8.8)	11.2 (8.5)	25.72 (7.54)	17.29 (10.47)	20.5 (5.9)
Lethargy/Social WD	11.4 (8.2)	11.1 (8.0)	16.56 (8.51)	12.22 (9.08)	11.3 (4.9)
Hyperactivity	20.2 (11.7)	20.2 (11.2)	32.2 (9.09)	33.22 (8.77)	26.1 (12.2)
Stereotypy	7.2 (4.8)	7.2 (4.5)	9.78 (4.74)	7.79 (6.01)	5.4 (4.5)
Inappropriate Speech	5.3 (3.7)	5.0 (3.7)	5.67 (3.92)	6.01 (3.94)	4.8 (3.6)

Dosing

- All participants began with 2·5 mg/d.
- Maximal dose was 20 mg.
- Dose schedule was followed unless the 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 dose could be lowered in 2·5 mg increments.
- Compliance was assessed by diary and medication returned.

DOSES

	Citalopram (n=73)	Placebo (n=76)	pvalue*
Baseline - Week 2			
n	**69**	71	0.1296
Mean (Std Deviation)	**3.12 (1.09)**	3.45 (1.49)	
Week 2 - Week 4			
n	**68**	66	0.0929
Mean (Std Deviation)	**5.96 (2.41)**	6.70 (2.71)	
Week 4 - Week 6			
n	**66**	65	0.0704
Mean (Std Deviation)	**8.42 (3.43)**	9.58 (3.82)	
Week 6 - Week 8			
n	**60**	62	0.0181
Mean (Std Deviation)	**11.1 (4.66)**	13.2 (4.79)	
Week 8 - Week 10			
n	**52**	59	0.1753
Mean (Std Deviation)	**14.7 (6.18)**	16.1 (4.65)	
Week 10 - Week 12			
n	**54**	54	0.0496
Mean (Std Deviation)	**16.5 (6.54)**	18.5 (3.45)	

THOM… …L.A.,
M…

A substantial minority of responders (7/17 of responders and 10/28 treated subjects) could not tolerate a 10-mg dose. This sensitivity was best illustrated by a subject who previously had a reaction of extreme aggressiveness and insomnia when put on 10 mg paroxetine. Before this subject came to the study, he had subsequently been put on lithium and risperidone with some response but had side effects as well as continuing to have significant obsessions and compulsions. After he was tapered off his medications, he was titrated up to the 5-mg dose of escitalopram and had a reaction similar to that reported with paroxetine (but without insomnia). His dose was reduced to his highest previously tolerated dose (2.5 mg), at which he showed substantial improvement and was successfully continued on this monotherapy for more than 20 weeks since the end of his participation in the study.

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Progress in Neuro-Psychopharmacology & Biological Psychiatry 29 (2005) 952 – 956
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Effect of age and gender on citalopram and desmethylcitalopram steady-state plasma concentrations in adults and elderly depressed patients

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Table 2
Mean (S.D.) citalopram (CIT) and desmethylcitalopram (DCIT) plasma concentrations (corrected for a daily dose of 20 mg), and CIT to DCIT ratios measured in different groups of patients receiving citalopram

	Group A = < 64 years (n = 48)	Group B 65 – 79 years (n = 57)	Group C > = 80 years (n = 23)	Men (n = 50)	Women (n = 78)	All patients (n = 128)	A vs. B	A vs. C	B vs. C	Men vs. women
CIT (ng/ml)	42 (17)	58 (24)	65 (30)	49 (25)	53 (26)	51 (26)	p < 0.001	p < 0.001	NS	NS
DCIT (ng/ml)	16 (9)	19 (8)	22 (10)	16 (8)	18 (9)	17 (9)	NS	p < 0.05	NS	NS
CIT + DCIT (ng/ml)	58 (21)	77 (28)	86 (36)	65 (28)	73 (31)	70 (30)	p < 0.001	p < 0.001	NS	NS
CIT/DCIT	3.2 (2.0)	3.6 (1.8)	3.1 (1.1)	3.6 (2.1)	3.1 (1.5)	3.3 (1.8)	NS	NS	NS	NS

NS: not significant.

Safety Measures:

- Treatment-Emergent adverse effects were elicited at each bi-weekly visit by the treating clinician using the Safety Monitoring Uniform Report Form (SMURF), a semi-structured review of body systems.
- Vital signs (pulse, blood pressure) and weight were measured at each visit.
- Blood for CBC, electrolytes, liver functions, were obtained at week 12.

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

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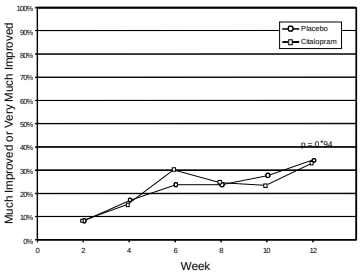
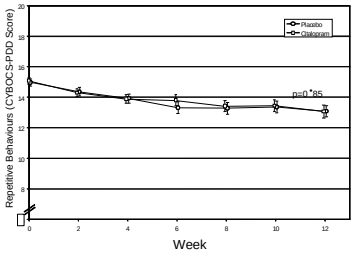
Adverse Event[a]	No. (%) Citalopram Hydrobromide–Treated Group (n=73)	Placebo Group (n=76)	*P* Value[b]
Any adverse event	71 (97.3)	66 (86.8)	.03
Neuropsychiatric Disorders			
Energy level increased	28 (38.4)	15 (19.7)	.02
Anger or irritability	18 (24.7)	13 (17.1)	.31
Aggression or hostility	17 (23.3)	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
Gastrointestinal Disorders			
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
Sleep Disturbance			
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
Infections and Infestations			
Cold, flu, or other systemic infection	31 (42.5)	26 (34.2)	.32
Metabolism and Nutrition Disorders			
Appetite decreased	11 (15.1)	10 (13.2)	.82
Appetite increased	7 (9.6)	8 (10.5)	>.99
Skin and Subcutaneous Tissue Disorders			
Rash	12 (16.4)	8 (10.5)	.34
Other skin or subcutaneous tissue disorder	9 (12.3)	1 (1.3)	.01
General Disorders			
Fatigue	10 (13.7)	10 (13.2)	>.99
Immune System Disorders			
Allergies	15 (20.5)	11 (14.5)	.39
Respiratory, Thoracic, and Mediastinal Disorders			
Cough	10 (13.7)	5 (6.6)	.18
Serious Events			
Any serious adverse event	1 (1.4)	0	.49



Percentage of Children with a Rating of Much Improved or Very Much Improved on the Clinical Global Impressions — Improvement Scale (CGI-I) During the 12-Week Trial.
All children assigned to citalopram (n = 73) and to placebo (n = 76) are included. Week 2 is the first opportunity to assess change from baseline.



Mean CYBOCS-PDD Scores Over Time for Citalopram and Placebo.
Scores reflect frequency and intensity of repetitive behaviours and are shown with standard error. All children assigned to citalopram (n = 73) and to placebo (n = 76) are included.

Compulsive and Repetitive Behaviors Over Time in the Trial by Treatment Group

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

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.

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Compulsive and Repetitive Behaviors Over Time in the Trial by Treatment Group

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		
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

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Conclusions

- Citalopram was not superior to placebo in this sample of children with autism spectrum disorders.
- Neither the rate of positive global response to citalopram, nor dimensional scores of repetitive behaviors on the blinded clinician-rated CYBOCS-PDD nor the parent-rated RBS-R suggested any difference between groups.

STAART psychopharm group

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