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Atomoxetine for Attention-Deficit/Hyperactivity Disorder Symptoms in Children with Pervasive Developmental Disorders: A Pilot Study

Pieter W. Troost, M.D., Ph.D.,[1] Mark-Peter Steenhuis, M.S.,[1]
Hanneke G. Tuynman-Qua, M.D.,[2] Luuk J. Kalverdijk, M.D.,[1]
Jan K. Buitelaar, M.D., Ph.D.,[3] Ruud B. Minderaa, M.D. Ph.D.,[1]
and Pieter J. Hoekstra, M.D., Ph.D.[1]

ABSTRACT

Objective: **This pilot study examined the effects of atomoxetine on attention-deficit/hyperactivity disorder (ADHD) symptoms and autistic features in children with pervasive developmental disorders (PDD).**

Method: **Twelve children (aged 6–14 years) with PDD accompanied by ADHD symptoms entered a 10-week open-label study with atomoxetine (1.19 ± 0.41 mg/kg/day). Response was assessed by using parent and clinician rating scales with change in the ADHD-Rating Scale (ADHDRS) as primary outcome measure.**

Results: **Atomoxetine reduced ADHD-symptoms as measured by the ADHDRS (44% decrease vs. baseline, $p < 0.003$), the Conners' Parent Rating Scale—R:S (CPRS-R) (25% in the subscale "Cognitive Problems," $p < 0.028$; 32% in "Hyperactivity," $p < 0.030$; and 23% in "ADHD index," $p < 0.023$). We found a reduction of 21% ($p = 0.071$) for changes in the subscale "Hyperactivity" of the Aberrant Behavior Checklist (ABC). No change was found in any of the other ABC subscales, nor in the subscale "Oppositional" of the CPRS-R. Five patients (42%) discontinued because of side effects. Gastrointestinal symptoms, irritability, sleep problems, and fatigue were the most frequent side effects.**

Conclusions: **These preliminary findings indicate that atomoxetine may be a promising new agent in the treatment of ADHD symptoms in children with PDD. However, children with PDD may have a higher vulnerability for some of the known side-effects of atomoxetine.**

INTRODUCTION

Children with pervasive developmental disorders (PDD's) are characterized by marked impairments in social interaction and communication, and often show restricted repetitive and stereotyped patterns of behavior (Volkmar et al. 2004). A wide range of pharmacological interventions are used to ameliorate some of the core and secondary features, amongst which

[1]Department of Psychiatry, University Medical Center Groningen, University of Groningen, The Netherlands.
[2]Dutch affiliate of Eli Lilly and Company.
[3]Department of Psychiatry, University Medical Center, St. Radboud, Nijmegen, The Netherlands.

inattention and overactivity are the most frequently targeted symptoms (Buitelaar and Willemsen-Swinkels 2000; Aman 2004). It is estimated that up to 20% of children with autistic disorder are prescribed stimulant medication to treat such behavior (Aman et al. 1995). However, these children appear to be particularly susceptible to some of the well-known side effects of these agents. For example, earlier studies found that methylphenidate could worsen social withdrawal, dullness, stereotypies, and tics, and increase aggression and agitation when used in hyperactive children with autistic disorder (Aman 1996; Handen et al. 2000). In a recent double-blind, controlled dosage study of immediate-release methylphenidate in 66 children with pervasive developmental disorders and hyperactivity/impulsivity, about half of the participants responded to at least one of the doses. Effect sizes, however, were modest and almost 10% of the children discontinued treatment due to adverse events (RUPP 2005). These side effects significantly limit the feasibility of psychostimulants in children with PDD.

Also, while the classical antipsychotics such as haloperidol (Anderson et al. 1989) and the now frequently used atypical antipsychotic agent risperidone have been shown to reduce overactivity (RUPP 2002; Troost et al. 2005), they do not appear to bring about improvements in distractibility, inattention, or learning, as well expose children to risks for long-term unwanted effects, including weight gain and neurological side effects.

In the treatment of ADHD, several other nonstimulant medications have been used, including desipramine, bupropion, clonidine, guanfacine, and fenfluramine (Biederman and Spencer 2000; Scahill et al. 2001; Spencer et al. 2002). Experience with these nonstimulant medications in autistic and developmentally disabled populations is limited (Biederman et al. 1989; Jaselskis et al. 1992; Aman et al. 1993; Conners et al. 1996; Posey et al. 2004). Although some supportive evidence exists for its use in the treatment of attention-deficit/hyperactivity disorder (ADHD) in general, overall, a meager database, safety concerns, or both limit their use.

A promising new group of medications for the treatment of ADHD symptoms are the noradrenergic reuptake inhibitors. There is a theoretical basis for a noradrenergic influence on attention and executive functions (Pliszka et al. 1996), and compounds influencing noradrenergic pathways are known to be effective in the treatment of ADHD (Biederman and Spencer 1999; Prince et al. 2000). One of the more recent examples of this group is atomoxetine, a potent inhibitor of the presynaptic norepinephrine transporter. Atomoxetine has been shown to be superior to placebo in treating ADHD symptoms and is in general well tolerated in pediatric and adult studies (Spencer et al. 1998; Michelson et al. 2001; Buitelaar et al. 2004; Michelson et al. 2004). In one study where atomoxetine was compared to methylphenidate, the response rate did not differ significantly (Kratochvil et al. 2002).

Atomoxetine is of particular interest for the treatment of PDD from the perspective of its possible enhancing effect on social behavior in depressed patients and normal subjects (Tse and Bond 2002). To date, only one small study retrospectively assessed the effect of atomoxetine in 20 children and adolescents with PDD, of whom 12 patients appeared to respond favorably (Jou et al. 2005). Therefore, the primary purpose of this study was to evaluate the tolerability and effectiveness of atomoxetine in the treatment of attention problems, hyperactivity, and impulsivity in children with PDD, whereas as a secondary purpose we sought to evaluate the possible response to atomoxetine on the core symptoms of PDD.

METHOD

Subjects

Study participants who were 6–17 years of age were recruited from referred patients of the Groningen University Child and Adolescent Psychiatry Center and the Youth Department of the Groningen Center for Mental Health, both ambulatory centers. All children had to meet *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, text revision (DSM-IV-TR) criteria (American Psychiatric

Association 2000) for a PDD, that is, autistic disorder, Asperger's disorder, or a PDD not otherwise specified (PDDNOS). These diagnoses were established by clinical assessment, corroborated by algorithm cutoff scores on the Autism Diagnostic Interview (ADI)-Revised. The ADI is a semistructured method of eliciting information from a parent to confirm a clinical impression of autism in children and adults. The interview was developed by Lord and colleagues (1994) and has demonstrated excellent reliability and validity for the diagnosis of autistic disorder (Rutter et al. 2003). Two interviewers were trained in administering and scoring the interview. All interviewers had reached 80% reliability in scoring the ADI-R, as required.

Moreover, patients were required to meet the DSM-IV-TR criteria for ADHD by clinical assessment and also had to have a symptom severity score at least 1.7 SD above age and gender norms on the total, the inattentive, or the hyperactivity/impulsive subscale scores on the ADHD Rating Scale-IV-Parent Version, Investigator Administered and Scored (ADHDRS) (DuPaul et al. 1998).

Children on effective psychotropic drug treatment for ADHD symptoms were excluded. Other exclusion criteria included an intelligence quotient lower than 70 as assessed by the Wechsler Intelligence Scale for Children, 3rd edition (Wechsler 1991), presence of a serious medical illness, of co-morbid psychosis or bipolar disorder, a history of seizure disorder, or ongoing use of psychoactive medications other than the study drug.

The aim and procedure of the study were fully explained to the subjects and their parents before the parents' written consent was requested. If the subject was 12 years or older, the written assent of the subject was obtained along with the consent of the parents. The study was reviewed and approved by the Groningen University Hospital's ethical review board and was in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Measures

Weekly ratings included the Investigator Administered and Scored ADHDRS, the Clinical Global Impression Scale of severity with regard to ADHD symptoms (CGI-ADHD-S), and the short form of the Conners' Parent Rating Scale—Revised (CPRS-R). The ADHDRS contains 18 items that correspond with the DSM-IV ADHD symptoms, whereby each item is scored on a 3-point scale, thus assessing the ADHD severity over the past week. The total score is computed as the sum of the scores on each of the 18 items (DuPaul et al. 1998). The CPRS-R is a 28-item rating scale completed by parents to assess problem behaviors related to ADHD (Conners 1997). The Aberrant Behavior Checklist (ABC) was rated every 2 weeks. The ABC is a well-validated instrument in specifically assessing PDD-related problems (Aman et al. 1985).

Safety and tolerability were assessed by weekly open-ended questioning for adverse events and monitoring of vital signs. Routine laboratory tests, electrocardiography, and physical evaluation were performed at pretreatment and at study end. All ECG's were reviewed by a child cardiologist.

Design and procedures

After an initial 3- to 28-day evaluation and medication wash-out period, patients were treated for 10 weeks with atomoxetine in an open-label fashion during the period from January through October, 2004. Atomoxetine was started at 0.5 mg/kg/day for 4 days, 0.8 mg/kg/day for 3 days, and furthermore titrated to a target dose of 1.2 mg/kg/day with flexibility of dose between 0.5 mg/kg/day and 1.8 mg/kg/day, on the basis of efficacy and tolerability. The total dose was administered as a single daily dose in the morning or as a twice daily divided dose, based on patient-preference or side effects.

Data analysis

The primary efficacy measure was the baseline to endpoint change in ADHDRS severity. Secondary analyses included change in CPRS-R and ABC subscores. Intent-to-treat analyses were applied to outcome measures from all patients enrolled for ongoing therapy. If a patient withdrew from the study prior to study

completion, data were examined by using the last observation carried forward model. Descriptive statistics were presented as mean ± SD. Differences between baseline and end-of-study were examined using Wilcoxon signed rank tests (two-tailed). In all tests, p values of less than 0.05 were used to indicate statistical significance. Effect sizes were computed to evaluate the magnitude of changes (Cohen 1988). As this was a pilot study, corrections for multiple comparisons were not made.

RESULTS

Subjects

Of the 47 patients who initially showed interest to participate, 20 did not meet inclusion criteria (9 patients did not meet DSM-IV-TR criteria for a PDD and/or ADHD, 7 patients because of efficacy of current psychotropic drug treatment for ADHD symptoms, 1 patient because of an intelligence quotient lower than 70, 1 patient was not able to swallow capsules, and 2 patients did not consent for a venipuncture) and 15 were unwilling to give final consent, mostly for logistic reasons. The remaining 12 patients (10 males), with a mean age of 10.2 ± 2.8 years (range 6–14 years) and a mean body weight of 41.4 ± 11.8 kg were enrolled and started open label treatment with atomoxetine. Six out of 12 children had a diagnosis of autistic disorder, 5 out of 12 a diagnosis of PDDNOS, and 1 child a diagnosis of Asperger's disorder. All patients had been treated the previous year with psychoactive medications, mostly psychostimulants (Table 1). Ten patients (83%) completed at least 6 weeks of the study, and 7 patients (58%) completed the whole study. Five patients (42%) discontinued because of side effects.

Psychometric measurements

Table 2 summarizes baseline and end-of-study ADHDRS, CPRS-R, and ABC scores of the intent-to-treat population. Statistically significant improvements were seen on the AHDHRS-Total score (Fig. 1), on the CPRS-R subscales "Hyperactivity," "Cognitive Problems," and "ADHD Index." Changes on the ABC only approached significance for improvement on the subscale "Hyperactivy" (p = 0.071); on the other scales no significant

Table 1. Clinical Characteristics of 12 Children Enrolled in an Open Label Treatment with Atomoxetine

Subject	*Age*	*Gender*	*DSM-IV-TR diagnosis of PDD*	*Mental development*	*Previous drugs*
1	14.7	M	Autistic disorder	Average IQ	Risperidone Methylphenidate
2	12.8	M	PDDNOS	Borderline IQ	Risperidone Methylphenidate Dextroamphetamine
3	7.2	M	Autistic disorder	Borderline IQ	Risperidone Methylphenidate Pipamperone
4	14.8	M	Autistic disorder	Borderline IQ	Methylphenidate
5	8.5	M	Autistic disorder	Borderline IQ	Quetiapine
6	8.7	M	Autistic disorder	Borderline IQ	Risperidone Methylphenidate
7	6.0	F	Autistic disorder	Borderline IQ	Risperidone Methylphenidate
8	11.8	M	PDDNOS	Borderline IQ	Pipamperone
9	9.3	M	PDDNOS	Borderline IQ	Clonidine Melatonin
10	8.6	M	Asperger's disorder	Average IQ	Dextroamphetamine
11	10.9	F	PDDNOS	Average IQ	Dextroamphetamine
12	9.3	M	PDDNOS	Average IQ	Methylphenidate Melatonin

TABLE 2. EFFICACY OUTCOMES AT BASELINE AND END OF STUDY FOR 12 CHILDREN WITH PERVASIVE DEVELOPMENTAL DISORDERS AND SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TREATED FOR UP TO 10 WEEKS WITH ATOMOXETINE[a]

Measure	*Baseline*	*End-of-Study*	p[b]	z	*ES*[c]
ADHD-Rating Scale-IV, Parent Version, Investigator Scored-Total score	40.33 ± 5.61	22.42 ± 9.49	0.003	−2.982	2.30
Conners' Parent Rating Scale-R: S subscales					
Oppositional subscale	9.17 ± 5.20	8.17 ± 5.59	0.609	−0.512	0.19
Cognitive Problems subscale	12.42 ± 4.83	9.33 ± 4.48	0.028	−2.197	0.66
Hyperactivity subscale	9.83 ± 3.93	6.67 ± 5.66	0.030	−2.169	0.65
Attention Deficit Hyperactivity Disorder Index	4.25 ± 0.91	18.67 ± 9.83	0.023	−2.273	0.63
Aberrant Behavior Checklist subscales					
Irritability	15.83 ± 9.45	14.50 ± 12.82	0.610	−0.511	0.12
Social Withdrawal	8.92 ± 5.85	7.17 ± 7.04	0.138	−1.483	0.27
Stereotypy	3.42 ± 3.09	2.58 ± 3.31	0.140	−1.476	0.26
Hyperactivity	23.58 ± 7.86	18.67 ± 13.78	0.071	−1.806	0.44
Inappropiate Speech	3.33 ± 2.61	3.75 ± 3.67	0.478	−0.710	−0.13

[a]Last observation carried forward. Mean ± SD.
[b]Comparison made with a two-tailed, Wilcoxon signed rank test.
[c]Effect sizes were calculated by dividing the difference in mean scores at baseline and end of study by the pooled standard deviation.

changes were apparent. Except for the ABC subscales "Inappropriate Speech" and "Irritability", all effect sizes were in the high range (> 0.14). At end of the study, all 7 (58%) completers and 2 (17%) noncompleters were rated as "much improved" or "very much improved" on the CGI-ADHD-S scale. The remaining 3 noncompleters were rated as

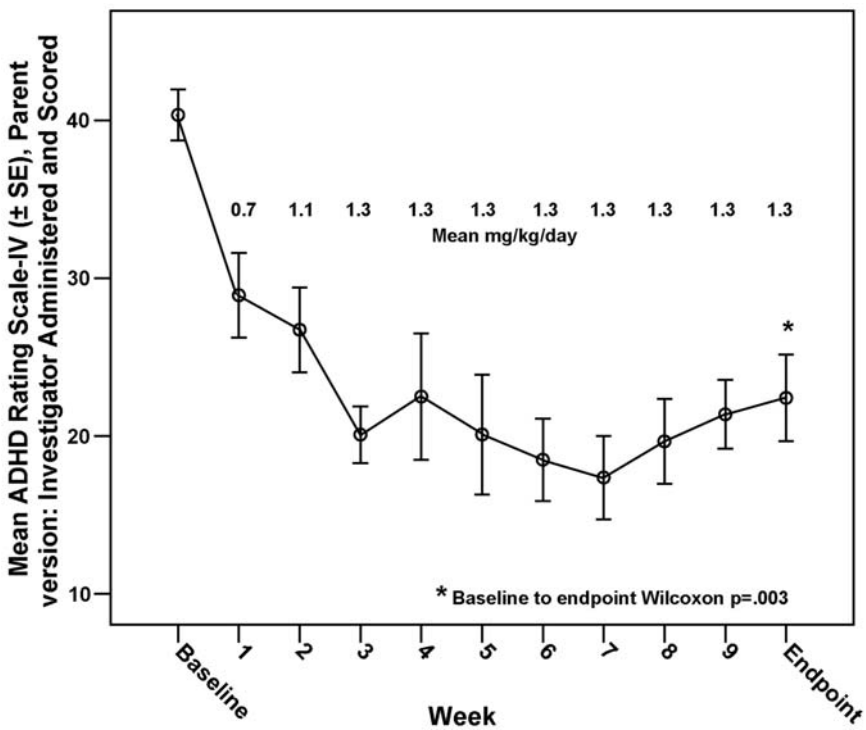

FIG. 1. Mean attention-deficit/hyperactivity disorder (ADHD) ratings by week in children with ADHD and pervasive developmental disorders (PDDs) on atomoxetine (n = 12).

"minimally improved" (8%), "no change" (8%), and "minimally worse" (8%) respectively.

Medication dosing and tolerability

The mean maximum total daily dose (TDD) of atomoxetine prescribed ranged from 0.49 mg/kg/day to 1.72 mg/kg/day, with an overall mean TDD of 1.19 ± 0.41 mg/kg/day. The actual TDD ranged from 17.5 mg/day to 80 mg/day. A total of 5 patients (42%) did not complete the study because of side effects: 1 patient after receiving one dose of atomoxetine because of nausea, 1 patient after 3 weeks because of anxiety, 1 patient after 6 weeks because of increased aggression/agitation, 1 patient after 8 weeks because of nausea/vomiting, and 1 patient after 9 weeks because of loss of appetite and (for the parents) unacceptable weight loss (3.3 kg). The most common side effects reported were anorexia (n = 10), irritability (n = 9), and sleeping problems (n = 7) (Table 3). All side effects were in the mild-to-moderate-range. Mean heart rate increased (85 vs. 93 beats per minute, baseline versus endpoint, respectively; $p < 0.022$), no differences were observed in blood pressure. Analysis of electrocardiograms (ECGs) revealed no evidence of effects of atomoxetine on mean conduction, repolarization, or rhythm (PR, QRS, and QTc intervals all unchanged). There were no clinically meaningful changes in vital signs and individual or mean laboratory test results, including liver function tests.

TABLE 3. SIDE EFFECTS REPORTED IN 12 CHILDREN WITH PERVASIVE DEVELOPMENTAL DISORDERS AND SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TREATED FOR UP TO 10 WEEKS WITH ATOMOXETINE[a]

Event	n	%
Anorexia	10	83
Irritability	9	75
Sleep problems	7	58
Drowsiness	4	33
Nausea	3	25
Constipation	3	25
Tearfulness	3	12
Tics	2	17
Rhinitis	2	17
Stomachache	2	17

[a]Incidence of Adverse Events Reported in at least 10% of atomoxetine-treated subjects.

DISCUSSION

To our knowledge, this is the first prospective study on the effectiveness of atomoxetine in children with PDD. The data of this open label pilot study suggest several preliminary findings. First, these findings indicate that atomoxetine may well be effective in reducing hyperactivity, inattention, and impulsivity in children with PDD. All 7 completers appeared to have derived substantial clinical benefit, and nearly all ADHD-related instruments showed a statistical improvement from baseline to end-of-study, with only improvement on the ABC subscale "Hyperactivity" being not significant (p = 0.071). This is in line with the findings of a recently completed retrospective study in 20 children and adolescents with PDD, in which almost two thirds of the subjects showed a beneficial response in the conduct, hyperactivity, inattention, and learning domains (Jou et al. 2005). We found no improvement, and no worsening either on any of the other ABC subscales, including "Irritability," "Stereotypy," and "Social Withdrawal." Also, there was no improvement on the "Oppositional" subscale of the CPRS-R. This indicates that atomoxetine may not be effective for any of the behavior problems that are frequently associated with PDD. There were no clinically meaningful changes in individual or mean laboratory tests, and in particular, given the recent warning in the Physician Package Insert (PI), there was no significant increase in liver function tests.

Also of note is that 5 out of 12 children terminated the study as a result of side effects: 3 children because of gastrointestinal complaints and the other 2 children due to anxiety and increased aggression. Although gastrointestinal symptoms such as loss of appetite, stomach ache, and vomiting are known side effects of atomoxetine, these have only infrequently led to discontinuation in nonautistic children (Gillberg et al. 2003). Apparently, chil-

dren with PDDs may be more vulnerable to experience atomoxetine-associated side effects than nonautistic children. This surely should be studied more extensively in future controlled studies involving a larger number of patients. Other reported side effects included sleeping problems, drowsiness, constipation, and increased heart rate, all in the mild-to-moderate-range. A relatively high proportion of children had symptoms of irritability, aggression, and tearfulness, which might be related to the symptom cluster of irritability, hostility, and suicidality, which has recently been listed in the PI of atomoxetine-specific comments. Whether these symptoms, or any of the other psychiatric side effects, were a true drug effect remains uncertain, given the nonplacebo-controlled nature of the study. Moreover, PDDs in itself are well known to be associated with a wide range of often fluctuating behavior problems such as aggression, sleep problems, anxiety, and extreme sensitivity to changes.

This study had some clear limitations that should be addressed in future studies. The number of patients was small and it was not blinded nor placebo controlled. The mean age was 10.2 years, and more than 80% were male, making the findings possibly less accountable for adolescents and females. The population being studied included only relatively high-functioning subjects, indicating the need for some cautiousness in generalizing the findings to the more impaired autism population.

In conclusion, these preliminary findings indicate that atomoxetine may be a promising new agent in the treatment of ADHD symptoms not only in typically developing children but also in children with PDD. The possibly higher vulnerability of children with PDD for atomoxetine–associated side effects makes a slower dose titration advisable. However, these side effects should be viewed against the known problems associated with alternative medications (stimulants and antipsychotics) in patients with PDD. Clearly, the improvements observed in this trial call for future prospective double-blind studies involving larger numbers of participants.

DISCLOSURES

Dr. Buitelaar has been a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, UBC, Shire, Medice, Dr. Minderaa is a paid consultant to Eli Lilly and Janssen Cilag BV; Dr. Tuynman-Qua is an employee of Eli Lilly and Company; Dr. Kalverdijk has received support from Eli Lilly and Janssen Cilag BV; Drs. Troost and Hoekstra have received support from Eli Lilly; Mr. Steenhuis has no financial ties with for-profit enterprises.

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Address reprint requests to:
Pieter W. Troost, M.D., Ph.D.
Child and Adolescent Psychiatry Center
P.O. Box 660
9700 AR Groningen, The Netherlands

E-mail: p.troost@accare.nl