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Long-Term Treatment with Atomoxetine for Attention-Deficit/Hyperactivity Disorder Symptoms in Children and Adolescents with Autism Spectrum Disorder: An Open-Label Extension Study

Myriam Harfterkamp, MD, Jan K. Buitelaar, MD, PhD, Ruud B. Minderaa, MD, PhD, Gigi van de Loo-Neus, MD, Rutger-Jan van der Gaag, MD, and Pieter J. Hoekstra, MD, PhD

Abstract

Objective: The efficacy and tolerability of long-term treatment with atomoxetine for symptoms of attention-deficit/hyperactivity disorder (ADHD) in children with autism spectrum disorder (ASD) has not been established.

Methods: In this study, 88 patients 6–17 years of age, with ADHD and ASD, were treated with 1.2 mg/kg/day atomoxetine for 20 weeks as follow-up of an 8 week double-blind placebo-controlled period. Primary endpoint was the ADHD Rating Scale (ADHD-RS).

Results: After 8 weeks of initial treatment, the mean total, inattention, and hyperactivity-impulsivity ADHD-RS further decreased significantly from 34.9 to 27.0 for the total ADHD-RS, from 18.3 to 14.5 for the ADHD-RS inattention subscale, and from 16.5 to 12.6 for the hyperactivity-impulsivity subscale. Adverse events were mild and tended to diminish over time during continued treatment, especially regarding nausea and fatigue. There were no serious adverse events.

Conclusions: The results of the present analysis suggest that continued treatment with atomoxetine up to 28 weeks further improve ADHD symptoms in children and adolescents with ASD, while adverse events tend to subside. Future studies investigating the long-term efficacy of atomoxetine in children and adolescents with ASD should be randomized and placebo controlled.

This study has been registered in ClinicalTrials.gov (www.clinicaltrials.gov) under registration number NCT00380692.

Introduction

Atomoxetine, a noradrenergic reuptake inhibitor, has been shown in several clinical trials to be an effective and well tolerated treatment for attention-deficit/hyperactivity disorder (ADHD) in children and adolescents and adults (Michelson et al. 2002; Weiss et al. 2005). We recently performed a double-blind placebo-controlled 8 week trial with 97 children and adolescents with an autism spectrum disorder (ASD) and concomitant ADHD symptoms, and demonstrated superior efficacy of atomoxetine compared with placebo on symptoms of ADHD (Harfterkamp et al. 2012). As an extension to our 8 week placebo-controlled trial, we were interested to know if longer-term treatment beyond the initial 8 weeks, up to 28 weeks, would lead to further improvement in ADHD symptoms. To our knowledge, no studies on the efficacy of longer-term treatment with atomoxetine in children and adolescents with ASD have as yet been performed. In children and adolescents with typical ADHD, two double-blind, randomized placebo-controlled studies have shown that further improvement of ADHD symptoms through treatment with atomoxetine may be expected until up to 10–12 weeks of treatment (Montoya et al. 2009; Svanborg et al. 2009). An integrated database, created by pooling data from 13 clinical trials (6 double-blinded placebo-controlled and 7 open-label studies) showed a gradual clinical response up to 3 months, at which point symptoms stabilized (Wilens et al. 2006). Also, a meta-analysis of 13 different studies showed improvement in ADHD symptoms in young children with typical ADHD to continue to increase up to 12 months (Kratochvil et al. 2006). The long-term effects of atomoxetine in children and adolescents with typical ADHD were

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Data analyses were done by Myriam Harfterkamp and Pieter J. Hoekstra.

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confirmed in placebo-controlled discontinuation studies after several months of atomoxetine treatment (Michelson et al. 2004; Buitelaar et al. 2007).

We also aimed to investigate the course of adverse events at continued treatment. In a pooled study of 13 double-blind, placebo-controlled trials and 3 open-label studies of 714 children and adolescents with ADHD on atomoxetine for ≥3 years, there were no new or unexpected adverse events compared with acute treatment. Common adverse events such as gastrointestinal complaints, somnolence, and irritation or aggression were most frequent in the first month of treatment and tended to subside thereafter (Donnelly et al. 2009). In the present study, we asked whether adverse events as observed after 8 weeks of treatment would diminish over time in children and adolescents with ASD and concomitant ADHD.

We hypothesized that continued treatment with atomoxetine for ADHD symptoms in children and adolescents with ASD beyond 8 weeks would be associated with further decrease of clinician-rated ADHD symptoms, whereas we expected adverse events to subside over time. All patients who had completed our placebo-controlled trial were offered open-label extension for 20 weeks, resulting in a group of patients with 20 weeks (the original placebo group) and another group with 28 weeks of active treatment duration (the original atomoxetine group).

Materials and Methods

Study design

This study reports the results of a 20 week open-label extension treatment with atomoxetine up to 1.2 mg/kg/day in children and adolescents with both ASD and ADHD who had participated in an 8 week randomized double-blind multicenter trial of atomoxetine versus placebo. Patients who had completed the placebo-controlled trial entered the open-label extension phase without disclosing the treatment allocation of the preceding 8 week trial.

Inclusion and exclusion criteria

For inclusion in the study, subjects had to be between 6 and 17 years, have an intelligence quotient (IQ) of at least 60 on a Wechsler Intelligence Scale (60 being an important limit for special education in the Netherlands), and have a clinical diagnosis of both ASD and ADHD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000). Presence of ASD was established by clinical assessment and corroborated by at least two scores on the Autism Diagnostic Interview Revised (ADI-R) (Rutter et al. 2003) above the cutoff, that is, >10 on the social interaction subscale, >8 on the communication and language subscale (for nonverbal subjects this had to be >7), and/or >3 on the restricted and repetitive behaviors subscale. ADHD diagnosis had to be in accordance with the DSM-IV-TR criteria A through D for ADHD any subtype. Assessment of ADHD was based on routine clinical procedures and corroborated by scores at least 1.5 standard deviations above the age norm for the diagnostic subtype, using published norms for the parent-based ADHD rating scale (ADHD-RS) (Faries et al. 2001). Nine Dutch child and adolescent psychiatry centers, six university centers (Amsterdam, Groningen, Leiden, Maastricht, Nijmegen, and Utrecht) and three non-university centers (The Hague, Hoorn, and Oosterhout) could recruit patients for the study.

Exclusion criteria included a weight of <20 kg; presence of psychosis, bipolar disorder, or substance abuse; a serious medical illness, history of seizures, ongoing use of psychoactive medications other than the study drug; and intended start of a structured psychotherapy or inpatient treatment. Apart from psychosis and bipolar disorder, all other forms of comorbidity were allowed for entering the study. Also, prior experience with ADHD medication was not an exclusion criterion. Participating patients who started psychoactive medication other than the study drug, structured psychotherapy, or inpatient treatment had to discontinue study participation.

Both parents and adolescents ≥12 years of age had to give written informed consent, whereas younger children had to assent. The study had been approved by the national and local institutional review board committees.

Dosing of atomoxetine

After completion of the 8 week trial, irrespective of subjects’ treatment allocation, dosing of atomoxetine in all subjects started at 0.5 mg/kg/day for 1 week, was increased to 0.8 mg/kg/day the week thereafter, and then increased to the final maximum once daily dose of 1.2 mg/kg/day. The dose of atomoxetine could be lowered to 0.8 mg/kg/day based on tolerability. In the previous 8 week double-blind trial, placebo or atomoxetine had been titrated in 3 weeks to a fixed once-daily dose of 1.2 mg/kg/day. Doses were rounded up or down to the closest available strength, using capsules of 5, 10, 20, 25, and/or 40 mg. At the end of the study, the group originally allocated to atomoxetine had received 28 weeks of treatment and the group originally allocated to placebo had received 20 weeks of treatment.

Measurements

As an efficacy measure, we used the investigator-rated ADHD-RS based on parents’ report, a DSM-IV-TR based rating scale that assesses symptom severity over the past week using 18 items on inattentive and hyperactive-impulsive symptoms to be scored on a four-point scale (0 = never, 1 = sometimes, 2 = often, 3 = very often). The total score is computed as the sum of the scores on each of the 18 items. Inattention and hyperactivity-impulsivity subscale scores only sum the scores of the respective items (Du Paul et al. 1998). All raters had been trained in applying the ADHD-RS and in almost all cases; each subject was rated by the same assessor throughout the study.

Safety was assessed at each visit by open-ended questioning for adverse events. A serious adverse event was defined as death, a life-threatening symptom, disability, or hospitalization.

Data analysis

We aimed to investigate changes in ADHD-RS upon continued treatment with atomoxetine after 8 weeks of initial treatment. For the group who had originally been allocated to atomoxetine, we had assessments after 8, 13, 16, and 28 weeks of treatment with atomoxetine. For the group originally allocated to placebo, we had assessments after 8 and 20 weeks of treatment with atomoxetine.

Changes from 8 weeks of treatment of ADHD-RS were analyzed using linear mixed-model analyses for both groups together. Also, as additional analyses, we assessed changes in ADHD-RS for all patients between the time points of 8 weeks and continued treatment for another 12 weeks (original placebo group) or 8 weeks (original atomoxetine group) with a paired-sample t test; thus, we made comparisons between 8 weeks of treatment and 16 or 20 weeks (merged into one group). Finally, for only the group
All analyses were conducted on the full data set including all patients receiving at least one dose of the study drug after the initial 8 week treatment period. The repeated measures ANOVAs and paired-sample t tests followed the intent-to-treat principle, by using last observation carried forward. We used a p value <0.05 to indicate statistical significance.

Results

Study participants

Of the 97 subjects who were enrolled in the 8 week placebo-controlled trial, 88 continued in the open-label extension phase (42 of 48 previously on atomoxetine and 46 of 49 previously on placebo). Seventy-three subjects remained on atomoxetine during the entire planned extension phase; 15 discontinued for a variety of reasons. Figure 1 shows the flow of participants through the study, including the placebo-controlled part. Table 1 shows baseline characteristics of study participants. Participants were enrolled in the placebo-controlled study from October 2006 to March 2008.

Effects of longer term treatment on ADHD severity

For the whole group of patients, the mean total, inattention, and hyperactivity-impulsivity ADHD-RS decreased significantly between the time points of 8 weeks of initial treatment and continued treatment. Over all subjects, the mixed-model analyses showed a significant average decrease per week on the total ADHD-RS of 0.27 (95% CI 0.06–0.48; p = 0.01), on the ADHD-RS inattention subscale of 0.14 (95% CI 0.06–0.22; p < 0.001), and on the ADHD-RS hyperactivity-impulsivity subscale of 0.13 (95% CI 0.08–0.18; p = 0.05).

These results were confirmed by using classical repeated measurements analyses. When comparing 8 initial weeks of treatment to another 12 weeks (original placebo group) or 8 weeks (original atomoxetine group), the total ADHD-RS decreased significantly from 34.9 (SD 10.5, range 6–54) to 27.0 (SD 12.1, range 5–54), paired-sample t test t = 7.8; df = 87; p < 0.001; the inattention subscale of the ADHD-RS from 18.3 (SD 5.5, range 3–27) to 14.5 (SD 6.3, range 2–27), paired-sample t test t = 7.1; df = 87; p < 0.001; and the hyperactivity-impulsivity subscale of the ADHD-RS from 16.5 (SD 6.5, range 0–27) to 12.6 (SD 6.9, range 0–25).

### Table 1. Baseline Characteristics of Participants with Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder in a 20 Week Open-Label Extension Treatment with Atomoxetine Following an 8 Week Randomized Double-Blind Trial of Atomoxetine Versus Placebo

<table>
<thead>
<tr>
<th></th>
<th>Subjects who started with atomoxetine (n=42)</th>
<th>Subjects who started with placebo (n=46)</th>
<th>Whole group (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; mean (SD), range, years</td>
<td>10.0 (2.8), 6–16</td>
<td>10.0 (3.0), 6–17</td>
<td>10.0 (2.9), 6–17</td>
</tr>
<tr>
<td>Male gender; n(%)</td>
<td>37 (88.1%)</td>
<td>39 (84.8%)</td>
<td>76 (86.3%)</td>
</tr>
<tr>
<td>Overall IQ (Wechsler); mean (SD), range</td>
<td>92.5 (16.9), 65–132</td>
<td>93.6 (17.8), 61–138</td>
<td>93.1 (17.3), 61–138</td>
</tr>
<tr>
<td>No previous psychopharmacological treatment for ADHD; n(%)</td>
<td>15 (35.7%)</td>
<td>17 (37.0%)</td>
<td>32 (36.3%)</td>
</tr>
<tr>
<td>CGI-ADHD-S; mean (SD), range</td>
<td>5.0 (0.73), 3–7</td>
<td>5.1 (0.88), 3–7</td>
<td>5.0 (0.80), 3–7</td>
</tr>
<tr>
<td>Autistic disorder; n(%)</td>
<td>20 (47.6%)</td>
<td>31 (67.4%)</td>
<td>51 (58.0%)</td>
</tr>
<tr>
<td>Asperger’s disorder; n(%)</td>
<td>3 (7.1%)</td>
<td>2 (4.3%)</td>
<td>5 (5.7%)</td>
</tr>
<tr>
<td>PDDNOS; n(%)</td>
<td>18 (42.9%)</td>
<td>12 (26.1%)</td>
<td>30 (34.0%)</td>
</tr>
<tr>
<td>No ASD; n (%)</td>
<td>1 (2.4%)</td>
<td>1 (2.2%)</td>
<td>2 (2.3%)</td>
</tr>
</tbody>
</table>

*Based on Autism Diagnostic Interview-Revised.

*These subjects had erroneously been included in the study.

SD, standard deviation; IQ, intelligence quotient; ADHD, attention-deficit/hyperactivity disorder; CGI-ADHD-S, Clinical Global Impressions of ADHD-Severity; PDDNOS, pervasive developmental disorder not otherwise specified; ASD, autism spectrum disorder.
The first 8 weeks of treatment compared with those reported in the serious adverse events occurred during the entire study period. Two subjects, originally allocated to placebo), Two subjects, to atomoxetine and 7 originally allocated to placebo). Two subjects, stopped because of adverse events (4 originally allocated and these two subjects completed the entire study. No ad

**Table 2. Results of Paired-Sample t Tests of ADHD Rating Scale Total and Inattention and Hyperactivity-Impulsivity Subscale Scores Between Consecutive Time Points for the Group Originally Allocated to Atomoxetine**

<table>
<thead>
<tr>
<th>Total treatment length with atomoxetine</th>
<th>Total ADHD-RS Mean (SD) Paired samples t test statistics b</th>
<th>Inattention ADHD-RS subscale Mean (SD) Paired samples t test statistics b</th>
<th>Hyperactivity-Impulsivity ADHD-RS subscale Mean (SD) Paired samples t test statistics b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>40.3 (7.1)</td>
<td>20.6 (3.9)</td>
<td>19.7 (5.0)</td>
</tr>
<tr>
<td>8 weeks</td>
<td>32.4 (11.1)</td>
<td>16.9 (6.1)</td>
<td>15.5 (6.5)</td>
</tr>
<tr>
<td>13 weeks</td>
<td>t = 5.9; p &lt; 0.001</td>
<td>t = 5.1; p &lt; 0.001</td>
<td>t = 5.4; p &lt; 0.001</td>
</tr>
<tr>
<td>16 weeks</td>
<td>t = 3.5; p = 0.001</td>
<td>t = 3.5; p = 0.001</td>
<td>t = 2.7; p = 0.01</td>
</tr>
<tr>
<td>28 weeks</td>
<td>t = 1.8; p = 0.075</td>
<td>t = 1.2; p = 0.245</td>
<td>t = 1.9; p = 0.068</td>
</tr>
<tr>
<td>t = 2.5; p = 0.015</td>
<td>t = 2.6; p = 0.011</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Analyses were conducted on the full data set including all patients receiving at least one dose of the study, following the intent-to-treat principle, by using last observation carried forward.

**Adverse events**

Of the 88 subjects who started the 20 weeks open-label extension period, 11 stopped because of adverse events (4 originally allocated to atomoxetine and 7 originally allocated to placebo). Two subjects, both originally allocated to atomoxetine, were hospitalized (appendicitis and right pneumothorax) but there was no relation to the study drug, and these two subjects completed the entire study. No serious adverse events occurred during the entire study period. Table 3 shows the frequency of adverse events reported during the first 8 weeks of treatment compared with those reported in the subsequent 12 or 20 weeks of treatment. It is of note that both fatigue and nausea diminished in frequency upon continued treatment.

**Table 3. Adverse Events Reported in the First 8 Weeks of Treatment with Atomoxetine Compared with Continued Treatment of 12 or 20 Weeks**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Reported during first 8 weeks of treatment with atomoxetine (%) a</th>
<th>Reported during subsequent 12 or 20 weeks of treatment (%)</th>
<th>Significance level b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>6 (6.8%)</td>
<td>2 (2.3%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>11 (12.5%)</td>
<td>7 (8.0%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16 (18.2%)</td>
<td>8 (9.1%)</td>
<td>0.096</td>
</tr>
<tr>
<td>Early morning awakening</td>
<td>5 (5.7%)</td>
<td>1 (1.1%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (18.2%)</td>
<td>6 (6.8%)</td>
<td>0.041</td>
</tr>
<tr>
<td>Headache</td>
<td>18 (20.5%)</td>
<td>13 (14.8%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Influenza</td>
<td>5 (5.7%)</td>
<td>2 (2.3%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Initial insomnia</td>
<td>6 (6.8%)</td>
<td>6 (6.8%)</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (13.6%)</td>
<td>1 (1.1%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (6.8%)</td>
<td>5 (5.7%)</td>
<td>1</td>
</tr>
</tbody>
</table>

*aOnly those occurring in at least 5% of patients during the first 8 weeks of treatment.

*bProportion reported in first 8 weeks versus subsequent 12 or 20 weeks according to McNemar test.

**Discussion**

This study examined the effect of atomoxetine on ADHD symptoms in children and adolescents with ASD in an open-label extension period of 20 weeks after an 8 week placebo-controlled trial. Although results of the first 8 weeks period indicated better efficacy of atomoxetine compared with placebo with good tolerability (separately submitted article), the data of the present analysis suggest that continued treatment with atomoxetine up to a total treatment length of 28 weeks leads to further improvement of ADHD symptoms in children and adolescents with ASD. This is in contrast with the situation in children with typical ADHD, where no further improvement after 3 months of treatment is seen according to a pooled data analysis of 13 clinical trials (Wilens et al. 2006). Our findings therefore suggest that in patients with ASD and ADHD symptoms it takes clearly more time than in typical ADHD before their full response to atomoxetine has been established.

In the double-blind period of our study, atomoxetine appeared to have a more pronounced effect on hyperactivity-impulsivity than on inattention symptoms. Upon extended treatment up to 28 weeks, we found similar effects on both symptom domains. This relatively stronger long-term improvement of inattention is in line with...
previous findings indicating a somewhat stronger effect on inattention symptoms than on hyperactive impulsive symptoms after 6 months of treatment (Wilens et al. 2006; Adler et al. 2009).

Our data indicate that adverse events tended to diminish over increased treatment duration, especially with regard to nausea and fatigue, which both were clearly less frequently reported than during the first 8 weeks of treatment with atomoxetine. Also patients with typical ADHD have generally shown a reduction in adverse events over time (Kratochvil et al. 2006; Wilens et al. 2006; Donnelly et al. 2009). More than 75% of all patients starting the trial completed the whole study. Discontinuation because of adverse events occurred in 17.5% of all patients, mostly during the first 8 weeks of open label treatment. This is in remarkable agreement with the findings in the 6 month double-blind trial of treatment with atomoxetine in adults with ADHD (n=491), in which a discontinuation of 17.2% because of adverse events in the atomoxetine group was observed (Adler et al. 2009).

The most obvious limitations of the current are those associated with open label studies. The lack of a control group makes it hard to distinguish between natural course and regression toward the mean and true treatment effects. As a further limitation, we did not analyze teacher-based ratings, but relied solely on clinician-based overall ratings of ADHD symptoms. Another limitation has been the assessment of adverse events. We did not use standardized rating scales for this, but instead used open-ended questioning at every single visit and assumed that an adverse event had disappeared if it was not mentioned spontaneously by the children or parents anymore. We may thus have missed adverse events. However, our method of assessing adverse events is in line with previous trials involving atomoxetine. A final limitation may have been that our study sample had relatively few children with IQs in the lower range, making findings possibly less generalizable for this group.

Conclusions

The findings of the open-label extension of our placebo-controlled study suggest that continued treatment with atomoxetine for ADHD symptoms in children and adolescents with ASD beyond 8 weeks may lead to further improvement in both ADHD symptom domains of inattention and hyperactivity-impulsivity, whereas adverse events are generally mild and tend to subside over time. In other words, it may take up to half a year until full response to atomoxetine has been reached. Future studies investigating the long-term efficacy of atomoxetine in children and adolescents with ASD should be randomized and placebo controlled.

Clinical Significance

The presence of symptoms of ADHD in children and adolescents with ASD is a serious clinical problem and frequently complicates therapeutic management. Appropriate medication in patients with ADHD symptoms might enhance the patient’s ability to benefit from educational and behavior modification interventions. However, whereas the literature is full of studies on the efficacy of medications for ADHD, hardly any studies directed at ADHD symptoms in children and adolescents with ASD have been reported. Our study suggests that atomoxetine is effective on ADHD symptoms in children and adolescents with ASD and is well tolerated, with ongoing improvement during continued treatment.

Acknowledgments

We thank all participating sites in the Netherlands.

Disclosures

Myriam Harfterkamp has accepted invitations for congress travels from Eli Lilly, Ruud B. Minderaa was advisor for Eli Lilly. Jan K. Buitelaar has been a consultant to and member of advisory board of, and/or speaker for Janssen Cilag B.V., Eli Lilly, Bristol-Myer Squibb, Organon/Shering Plough, UCB, Shire, Medice, Servier, and Servier. Gigi van de Loo-Neus has received honoraria for presentations or advice over the past 2 years from the pharmaceutical companies Eli Lilly, UCB Pharma B.V., and Eurocept B.V. Rutger-Jan van der Gaag has no financial disclosures. Pieter J. Hoekstra has received funding through ZonMw, EU Seventh Framework Program, and National Institute of Mental Health as well as honoraria for presentations or advice from the pharmaceutical companies Desitin, Shire, and Eli Lilly.

References


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