Research on atomoxetine in Dutch ASD/ADHD children

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The RADAR study

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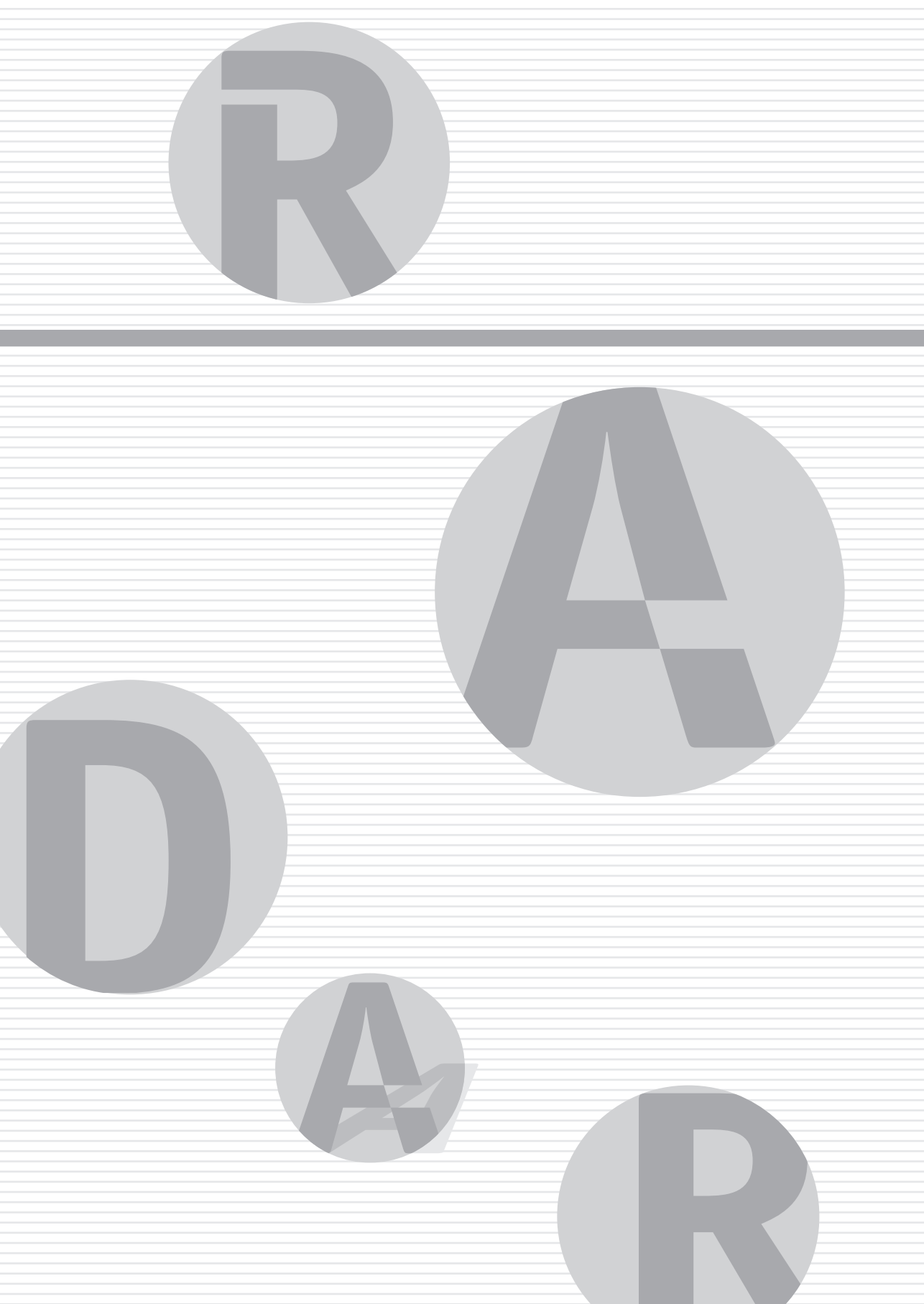
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Chapter 1

Introduction

Symptoms of Attention Deficit Hyperactivity Disorder in Autism Spectrum Disorder

Individuals with Autism Spectrum Disorder (ASD) have an impairment in social relatedness and verbal and non-verbal communication, such as responding inappropriately in conversations, misreading non-verbal interactions, or having difficulty building reciprocal social relationships and friendships appropriate to their age. In addition, people with ASD may be overly dependent on routines, highly sensitive to changes in their environment, and/or intensely preoccupied with certain interests or topics. ASD forms a continuum of developmental disorders, with some affected persons showing mild symptoms and others having much more severe symptoms. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition text revision (DSM-IV-TR) distinguishes five separate disorders: (1) autistic disorder, (2) Rett's disorder, (3) childhood disintegrative disorder, (4) Asperger's disorder, and (5) pervasive developmental disorder not otherwise specified. In the DSM-5 there is only one ASD category, which encompasses the previous DSM-IV categories autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified. Rett's disorder is a discrete neurologic disorder and no longer included within DSM-5, although patients with Rett's disorder may have ASD (Hymann 2013). The DSM-5 algorithm was reported to identify 91% of children with clinical DSM-IV-TR ASD diagnoses (Huerta, Bishop et al. 2012).

ASD has in general onset before the age of 3 and often lasts throughout a person's life, although symptoms typically change over time. Boys are 3-4 times more affected than girls (Hinkka-Yli-Salomäki, Banerjee et al. 2013). In the last decade there has been an increase in the incidence rate and prevalence of diagnosed ASD. It is unclear how much of this increase is due to a broader definition of ASD and better recognition or whether there has been a true increase in the number of people with ASD (Baird, Simonoff et al. 2006; Kim, Leventhal et al. 2011; Hansen, Schendel et al 2015). Most studies now report prevalence for ASD between 1 and 1.5% (US Centers for Disease Control and Prevention 2014; Kim, Leventhal et al. 2011)

Many children with ASD present with a range of co-occurring difficulties, such as presence of hyperactivity, self-injurious behavior, aggression towards others, and intolerance of change (Hill, Zuckerman et al. 2014). Also symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) are frequently present in ASD (Gadow, De Vincent et al. 2006; Rommelse, Franke et al 2010; Rommelse, Geurts et al. 2011). ADHD is characterized by a pattern of inattentiveness and/or hyperactive/impulsive behavior, present in multiple settings (e.g., school and home), and resulting in impairments in social, educational, and/or work settings. Symptoms include behaviors like failure to pay close attention to details, difficulty organizing tasks and activities, excessive talking, or

an inability to remain seated in appropriate situations. Whereas the DSM-IV-TR formally precludes a diagnosis of ADHD in patients with ASD, a wealth of clinical and population-based studies have pointed out that ADHD symptoms are common in children with ASD with rates varying from 41-78% (Gadow, DeVincent et al. 2006; Nijmeijer, Hoekstra et al. 2009; Murray 2010, Rommelse, Geurts et al. 2011). A DSM-5 ASD diagnosis now does not exclude a diagnosis of ADHD.

The presence of symptoms of ADHD in children with ASD is not only often a serious clinical problem, but may also complicate the therapeutic management of these children (Holtmann, Bolte et al. 2007; Sikora, Vora et al. 2012). Appropriate medication in patients with ASD with ADHD symptoms might enhance the child's ability to benefit from educational and behavior modification interventions (Gadow, De Vincent et al. 2006). However, while many studies have documented the efficacy of medications for ADHD (Sibley, Kuriyan et al. 2014), few medication studies on improving ADHD symptoms in children with ASD have been reported. Even less studies were primarily focused on ADHD symptoms in patients with ASD using medication registered for the treatment of these symptoms, i.e., psychostimulants or atomoxetine. Most randomized controlled trials were conducted with the atypical antipsychotics risperidone and aripiprazole, where severe irritability was the primary target of treatment and the benefit with regard to ADHD symptoms was a secondary outcome (Aman, Arnold et al. 2005; Shea, Turgay et al. 2004; Marcus, Owen et al. 2009; Owen, Sikich et al. 2009; Troost, Althaus et al, 2006; Aman, Hollway et al, 2008).

The overall objective of this thesis was to investigate the efficacy of atomoxetine, a non-stimulant component for the treatment of ADHD symptoms in children and adolescents with ASD.

Knowledge of psychopharmacological treatment of ADHD symptoms in children and adolescents with ASD

There are several options to pharmacologically address ADHD symptoms in children with ASD, which we briefly review below.

Psychostimulants

Psychostimulants act by blocking the dopamine transporter and norepinephrine transporter, leading to increased concentrations of dopamine and norepinephrine within the synaptic cleft, especially in the prefrontal cortex and the striatum. These agents are the first choice medical treatment for children and adolescents with ADHD, based on their large effect sizes and generally good tolerability (Graham, Banaschewski et al.

2011). The situation in children with ASD is somewhat different. Studies have shown that the effect of psychostimulants on ADHD symptoms in children with ASD is clearly lower when compared to children with only ADHD. Also, children with ASD have been shown to be more vulnerable to adverse events of psychostimulants, as confirmed by a publicly sponsored double-blind, placebo-controlled multicenter trial of methylphenidate (RUPP 2005; Quintana, Birmaher et al. 1995; Handen, Johnson et al. 2000).

Antipsychotics

Especially hyperactivity and impulsivity in children with ADHD are often associated with oppositional defiant behaviors and even aggression. Severe oppositional behavior and aggression that are maladaptive and do not respond to behavioral interventions are increasingly treated with antipsychotics, such as risperidone and aripiprazole. These two atypical antipsychotics received approval by the US Food and Drug Administration for the treatment of irritability in children with ASD. Efficacy of risperidone for the treatment of severe irritability in children with ASD has been demonstrated in randomized controlled trials both in the short term as well as after several months of treatment (Aman, Arnold et al. 2005; Shea, Turgay et al. 2004). Aripiprazole was also shown to be efficacious and well tolerated in an 8-week short-term treatment of severe irritability in children with ASD in two placebo-controlled studies (Marcus, Owen et al. 2009; Owen, Sikich et al. 2009). Although these studies also demonstrated an effect on hyperactivity, antipsychotics did not appear to have robust effects on distractibility, inattention, or learning, even though one study showed that risperidone had a beneficial effect after several months of treatment in enhancing divided attention in children with ASD (Troost, Althaus et al. 2006). Furthermore, atypical antipsychotics may expose children to risks of significant long-term side-effects, i.e., metabolic symptoms such as weight gain, glucose dysregulation, dyslipidemia, and increased risk of the metabolic syndrome (i.e., at least three of the five components are present: excess in abdominal fat, hypertriglicydemia, hyperglycemia, too low serum high-density-lipoproteins [HDL], and hypertension) Moreover, use of risperidone often causes long-lasting elevation of prolactin blood plasma levels, which may result in disturbed bone metabolism, calcium bone loss, and low bone density. A multiple-treatments meta-analysis showed that extrapyramidal symptoms, like tremor, psychomotor hyperactivity, akathisia, and dyskinesia are more common in typical anti psychotics, although they may still occur in the treatment with atypical antipsychotics such as risperidone and aripripazol (Leucht, Cipriani et al. 2013).

Alpha2-agonists

Guanfacine and clonidine are alpha-2-agonists which have been used alone or in combination with stimulants to decrease ADHD symptoms. Alpha 2-agonists inhibit the

release of norepinephrine into the synaptic cleft. Clonidine has been investigated in a small double-blind, placebo-controlled, crossover trial in eight children diagnosed with ASD and was associated with some improvement on hyperactivity albeit not clinically significant (Jaselskis, Cook et al. 1992). A retrospective open-label study seems to indicate some potential of guanfacine on reducing hyperactivity and attention problems, albeit with frequently occurring sedation (Posey, Puntney et al. 2004). A similar effect was found in an 8 week open label trial with guanfacine in a sample of 25 children with ASD (Scahill, Aman et al. 2006). A randomized, double-blind, multicenter, parallel-group, placebo controlled, dose optimization, efficacy and safety study was conducted between January 2011 and May 2013 in centers in Europe, the USA and Canada in which the efficacy (symptoms and function) and safety of dose-optimized extended release guanfacine was compared with placebo in children and adolescents with ADHD. Extended release guanfacine led to much stronger improvement of ADHD symptoms than placebo and was well tolerated (Hervas, Huss et al. 2014).

Guanfacine has, however, not been investigated in a randomized controlled trial in children with ASD.

Atomoxetine

In 2005 atomoxetine received a registration in the Netherlands for the treatment of ADHD in children and adolescents. This was based on several randomized controlled trials that had shown superior efficacy over placebo in reducing ADHD symptoms (Spencer, Biederman et al. 1998; Spencer, Biederman et al. 2002; Weiss, Tannock et al. 2005). Tolerability of atomoxetine appeared to be mostly favorable. Gastrointestinal problems, such as decreased appetite and abdominal pain, sleep problems, and fatigue are the most common atomoxetine related side-effects (Cheng, Chen et al. 2007). Also, treatment with atomoxetine is associated with increased pulse rate and blood pressure, albeit mostly not clinically relevant (Kratochvil, Wilens et al. 2006; Vaughan, Fegert et al. 2009). A large meta-analysis of all double-blind randomized controlled trials evaluating the efficacy and tolerability of atomoxetine for ADHD showed that atomoxetine treatment during four to 18 weeks was safe and superior to placebo (Schwartz and Corell, 2014), with on one hand more than 44% of the patients improving by >40%, but on the other hand nearly 40% failing to improve by at least 25%, thus confirming a bimodal response also found in a smaller meta-analysis (Newcorn, Sutton et al. 2009). Thus, there appears to be a subgroup, which continues to have significant ADHD symptoms despite treatment with atomoxetine.

Atomoxetine is an interesting compound for treating ADHD symptoms in patients with ASD, as it is a noradrenergic reuptake inhibitor, leading to an increase of norepinephrine, which may have an enhancing effect on social behavior, improved cooperation, and a reduction in self-focus (Tse and Bond, 2002).

Around 2005 some small scaled pilot studies investigated the effects of atomoxetine on ADHD symptoms in ASD, mostly with promising results. A small-scale, double-blind, placebo-controlled crossover study of atomoxetine in 16 children and adolescents with ASD reported atomoxetine to be superior to placebo on the primary outcome, the hyperactivity subscale of the Aberrant Behavior Checklist (p=0.043, effect size d=0.90). Upper gastrointestinal symptoms were the most common adverse events. All 16 patients on atomoxetine experienced mild upset stomach or nausea/vomiting versus five on placebo. Another common adverse event was fatigue, reported by 12 patients on atomoxetine versus 7 on placebo. Concomitant psychotropic medication was allowed in this study (Arnold, Aman et al. 2006). A retrospective open label study assessed the effect of atomoxetine in 20 children and adolescents of whom 12 patients appeared to respond favorably. Benefits were observed in the conduct, hyperactivity, inattention, and learning domains (Jou, Handen et al. 2005). In the department of child and adolescent psychiatry in Groningen, the Netherlands, a small open label pilot study was designed and implemented in which 12 children with ASD accompanied by ADHD symptoms received prospectively a 10 week open label treatment with atomoxetine. All seven completers of the study were "much" or "very much improved" on the Clinical Global Impression-Improvement scale (CGI-I). Five patients, however, discontinued because of adverse events, the most important being gastrointestinal symptoms, irritability, sleep problems, and fatigue (Troost, Steenhuis et al. 2006).

These first promising findings indicated that atomoxetine may be a worthwhile new agent in the treatment of ADHD symptoms in children and adolescents also affected with ASD. We therefore designed an adequately powered double blind placebo controlled study to confirm these preliminary findings, which led to the design of the study discussed in this thesis; **R**esearch on **A**tomoxetine in **D**utch **A**SD/ADHD Child**r**en (RADAR).

Research on Atomoxetine in Dutch ASD/ADHD Children (the RADAR study)

The RADAR study is a multicentered, randomized, double-blind, placebo-controlled, parallel group trial. Ninety-seven pediatric patients with ASD and ADHD symptoms have been enrolled.

Study design

The study consisted of three study periods (figure 1).

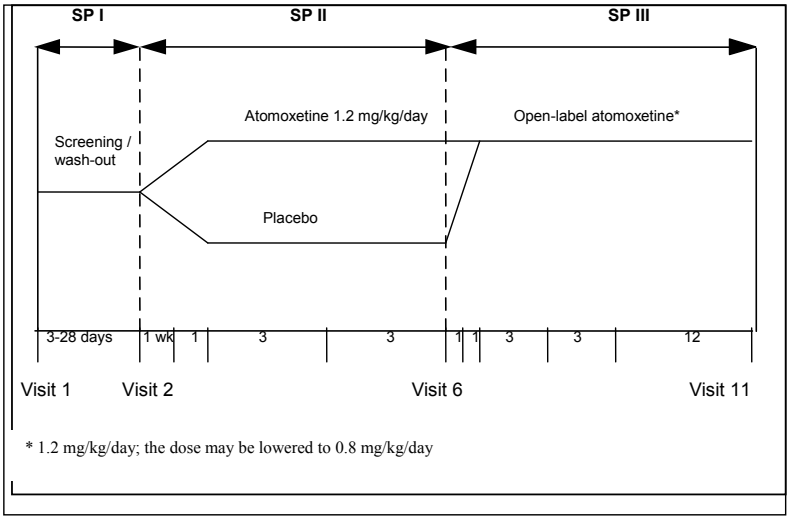

Figure 1 Illustration of the study design

In the first period possible candidates for inclusion in the study (children and adolescents between 6 and 17 years with a clinical diagnosis of ASD and concomitant ADHD symptoms) had been referred to one of nine participating 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). During this phase, patients were screened for eligibility. This assessment included a diagnostic evaluation to confirm both diagnoses of ASD and ADHD, cognitive testing, a thorough medical evaluation including a physical examination and health history. Also, a buccal swab was taken to determine Cytochrome P450 2D6 (CYP2D6) genotype.

For inclusion in the study children had to have a confirmed diagnosis of ASD and to have concomitant ADHD symptoms, plus an intelligence quotient (IQ) of at least 60 on a Wechsler Intelligence Scale (60 being an important limit for special education in the Netherlands). ASD diagnoses were confirmed through clinical assessment by certified child and adolescent psychiatrists (except in Oosterhout where this was done by a certified child neurologist) and had to be corroborated by algorithm cut-off scores on the Autism Diagnostic Interview Revised (ADI-R; Rutter, Le Couteur et al. 2003); that is, children had to have at least two ADI-R subscale scores above the cutoff, i.e., above 10 on the social interaction subscale, above 8 for verbal subjects and 7 for nonverbal subjects on the communication and language subscale, and/or above 3 on the restricted and repetitive behaviors subscale, thus operationalizing the whole range of ASD. To

ensure diagnostic consistency across sites, all ADI-R assessments were done by raters who had been trained in using and interpreting the ADI-R by a certified trainer. Study criteria of ADHD symptoms were in accordance with DSM-IV-TR criteria A through D for any type of ADHD, corroborated by scores of at least 1.5 standard deviations above the age norm for children's diagnostic subtype using published norms for the parent-based ADHD-Rating Scale (DuPaul, Anastopoulos et al. 1998; Faries, Yalcin et al. 2001).

Exclusion criteria included a weight of less than 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. Both parents and children of 12 years and older had to give written informed consent, while younger children had to give assent.

The second period in the study was an 8 week randomized, double blind, placebo controlled phase. Patients were randomized in a 1:1 ratio to receive either placebo or atomoxetine. Both atomoxetine and placebo were titrated in three weeks to a fixed once-daily dose of 1.2 mg/kg/day (first week: 0.5 mg/kg/day; second week: 0.8 mg/kg/day; third week 1.2 mg/kg/day). Atomoxetine and placebo were available as capsules and identical in appearance. Atomoxetine capsules contained 5, 10, 20, 25, or 40 mg. In order to preserve the blinding, all doses were given in two capsules which had to be taken together in the morning.

The third period was a 20 weeks open-label extension treatment with atomoxetine. All patients who had completed the placebo controlled period were invited to participate in this open-label extension. For all patients dosing of atomoxetine started at 0.5 mg/kg/day and the dose was increased up to 1.2 mg/kg/day. The dose of atomoxetine could be lowered to 0.8 mg/kg/day based on tolerability.

Objectives and Outcome Measures

1. Primary Objective

The primary objective of this study was to test the hypothesis that atomoxetine given at a dose up to 1.2 mg/kg/day (once daily) for 8 weeks would be superior to placebo in the treatment of symptoms of ADHD in in- and outpatients aged 6 through 17 years with a diagnosis of ASD.

The primary efficacy measure was change from baseline after 8 weeks of double-blind, placebo-controlled treatment on the total score of the investigator-administered ADHD-RS (DuPaul, Anastopoulos et al. 1998; Faries, Yalcin et al. 2001). This DSM-IV

based rating scale contains 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) and assesses symptom severity over the past week. 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. We obtained ADHD-RS ratings at baseline, after 5, and after 8 weeks of treatment.

2. Secondary Objectives

The secondary objectives of the study were as follows:

a. To assess the efficacy of acute treatment with up to 1.2 mg/kg/day atomoxetine versus placebo for 8 weeks on symptoms of ADHD as measured by Clinical Global Impression-ADHD-Improvement (CGI-ADHD-I) and the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S).
b. To assess the safety and tolerability of up to 1.2 mg/kg/day atomoxetine versus placebo for 8 weeks and of atomoxetine during open label follow up in pediatric patients with ASD and ADHD symptoms.
c. To assess the efficacy of maintenance treatment with atomoxetine during open label follow-up on symptoms of ADHD as measured by the ADHD Rating Scale-IV-Parent Version: investigator scored, CGI-ADHD-I and the CTRS-R:S.
d. To assess the effect of up to 1.2 mg/kg/day atomoxetine versus placebo for 8 weeks on ASD symptoms as measured by the Aberrant Behavior Checklist (ABC) and the Children's Social Behavior Questionnaire (CSBQ).
e. To assess the effects of up to 1.2 mg/kg/day atomoxetine versus placebo for 8 weeks on cognitive functioning as measured by the Amsterdam Neuropsychological Tasks (ANT).

Secondary outcome measures

a. The Clinical Global Impressions of ADHD-Improvement (CGI-ADHD-I) which measures the total improvement (or worsening) of a patient's ADHD symptoms from the beginning of treatment, regardless of whether or not improvement (or worsening) is thought to be due entirely to drug treatment (Guy 1976). Change is rated on a 7-point scale (1=very much improved; 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse). We classified ratings of 1 and 2 as improved and all other ratings as not improved.
b. The Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S), a 28-item questionnaire to be completed by the child's teacher to assess problem behaviors related to ADHD in the school setting (Conners, Sitarenios et al. 1998). It

includes subscales on oppositional behavior, hyperactivity, cognitive problems/ inattention, and an ADHD index.

c. The Aberrant Behavior Checklist (ABC), a 58-item scale which consists of five subscales, labeled Irritability (15 items); Lethargy/Social Withdrawal (16 items); Stereotypic Behavior (7 items); Hyperactivity (16 items), and Inappropriate Speech (4 items). The ABC was developed as a measure of treatment effects in patients with developmental disabilities. It has been frequently used in medication and behavioral intervention studies in patients with developmental disabilities and has been shown to be sensitive to the effects of treatment (Aman, Singh et al. 1985; Troost, Steenhuis et al. 2006; Karabekiroglu and Aman 2009).
d. The Children's Social Behavior Questionnaire (CSBQ) which consists of 49 items covering a broad range of features typical for ASD, from subtle social, communication, and repetitive behavioral impairments seen in children with milder forms of ASD to more severe autistic-like features, with an emphasis on the former (Hartman, Luteijn et al. 2006). Items are rated on a three point likert-type fashion (i.e., 0= does not apply at all; 1= applies slightly or infrequently; 2= applies clearly or often). The CSBQ consists of a total scale and six subscales: Subscale 1 Behavior/emotions not optimally tuned to the social situation (11 items); Subscale 2 Reduced contact and social interest (12 items); Subscale 3 Orientation problems in time, place, or activity (8 items); Subscale 4 Difficulties in understanding social information (7 items); Subscale 5 Stereotyped behavior (8 items); and Subscale 6 Fear of and resistance to changes (3 items). Multiple estimates of reliability and validity of the CSBQ were found to be good (Luteijn, Luteijn et al. 2000; Hartman, Luteijn et al. 2006; Bildt de, Mulder et al. 2009).
e. The Amsterdam Neuropsychological Tasks (ANT), a battery of computerized cognitive measurements. In the RADAR study four tasks were selected; baseline speech, focus attention, divided attention and eye-hand coordination (De Sonneville 2005).

Aim and context of this thesis

The primary aim of the current thesis was to compare the efficacy of atomoxetine versus placebo on ADHD symptoms in children with ASD. Furthermore, we investigated whether ADHD symptom improvement would be mediated by improvements in inhibitory control. Also, we investigated the possible effects of atomoxetine on ASD symptoms,

and we tried to identify predictors of positive treatment effects with atomoxetine.

Chapter 2 presents short-term efficacy and safety data. The primary objective was to test the hypothesis that atomoxetine would be superior to placebo in the treatment of symptoms of ADHD in patients with ASD as rated by the investigator-administered ADHD-RS (Faries, Yalcin et al. 2001). Secondary objectives were to assess the effects of atomoxetine versus placebo on overall change of ADHD as indexed by the Clinical Global Impression-Improvement scale rated by the investigator and on ADHD symptoms at school rated by the Conners Teacher Rating Scale-Revised: Short Form (CTRS-R:S) (Conners, Sitarenios et al. 1998). Furthermore we evaluated whether atomoxetine was safe and well tolerated in patients with ASD and ADHD symptoms. Safety was assessed by the same clinician who did the clinical ratings through open-ended questioning for adverse events by telephone after 1 and 2 weeks of treatment, and in person after 5 and 8 weeks of treatment. These were classified by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and judged to be related to the study drug or not. A serious adverse event was defined as death, life threatening, disability, or hospitalization. Adverse events that first occurred or worsened after study treatment started were defined as treatment-emergent adverse events.

Chapter 3 analyzed the effects of long term open label treatment with atomoxetine for ADHD symptoms in children with ASD. We included 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). We hypothesized that continued treatment with atomoxetine for ADHD symptoms in children with ASD beyond eight weeks would be associated with further decrease of clinician-rated ADHD symptoms, whilst we expected adverse events to subside over time.

Chapter 4 describes the comparison of atomoxetine and placebo on response inhibition and interference control. Our aims were to examine (1) whether atomoxetine improved 2 forms of inhibitory control (response inhibition and interference control) and (2) whether ADHD symptom improvement was mediated by improvements in inhibitor control.

Chapter 5 describes the effect of atomoxetine on ASD symptoms based on two parent-based rating scales; the Children's Social Behavior Questionnaire (CSBQ) and the Aberrant Behavior Checklist (ABC).

Chapter 6 describes a study to identify possible baseline predictors of responses of atomoxetine on ADHD symptoms.

Finally, in chapter 7 the findings as described in the previous chapters have been summarized and discussed. The thesis has been placed in a broader perspective, clinical perspectives have been described and suggestions for further research have been given.

Role of sponsor

The study was sponsored by Eli Lilly. Data analyses for the primary objective of this study described in Chapter 2 were performed by Alexander Schacht, PhD and Sireesha Pamulapati, PhD, both employees of Eli Lilly. The content of the paper of Chapter 2 was written by the primary authors in alignment with Eli Lilly and in accordance with the objectives as laid down in ClinicalTrials.gov (www.clinicaltrials.gov) under registration number NCT00380692.

In 2009, the complete data set of Eli Lilly was carried over to the researchers from the University Medical Center Groningen and the University of Groningen and of Karakter Child and Adolescent Psychiatry University Center Nijmegen, the Netherlands. The data analyses part of the secondary objectives described in Chapters 3-6 were done by Myriam Harfterkamp, Pieter J. Hoekstra, Dennis van der Meer, Jolanda van der Meer, Monika Althaus and Nanda Rommelse. Those papers were written without any involvement of Eli Lilly.

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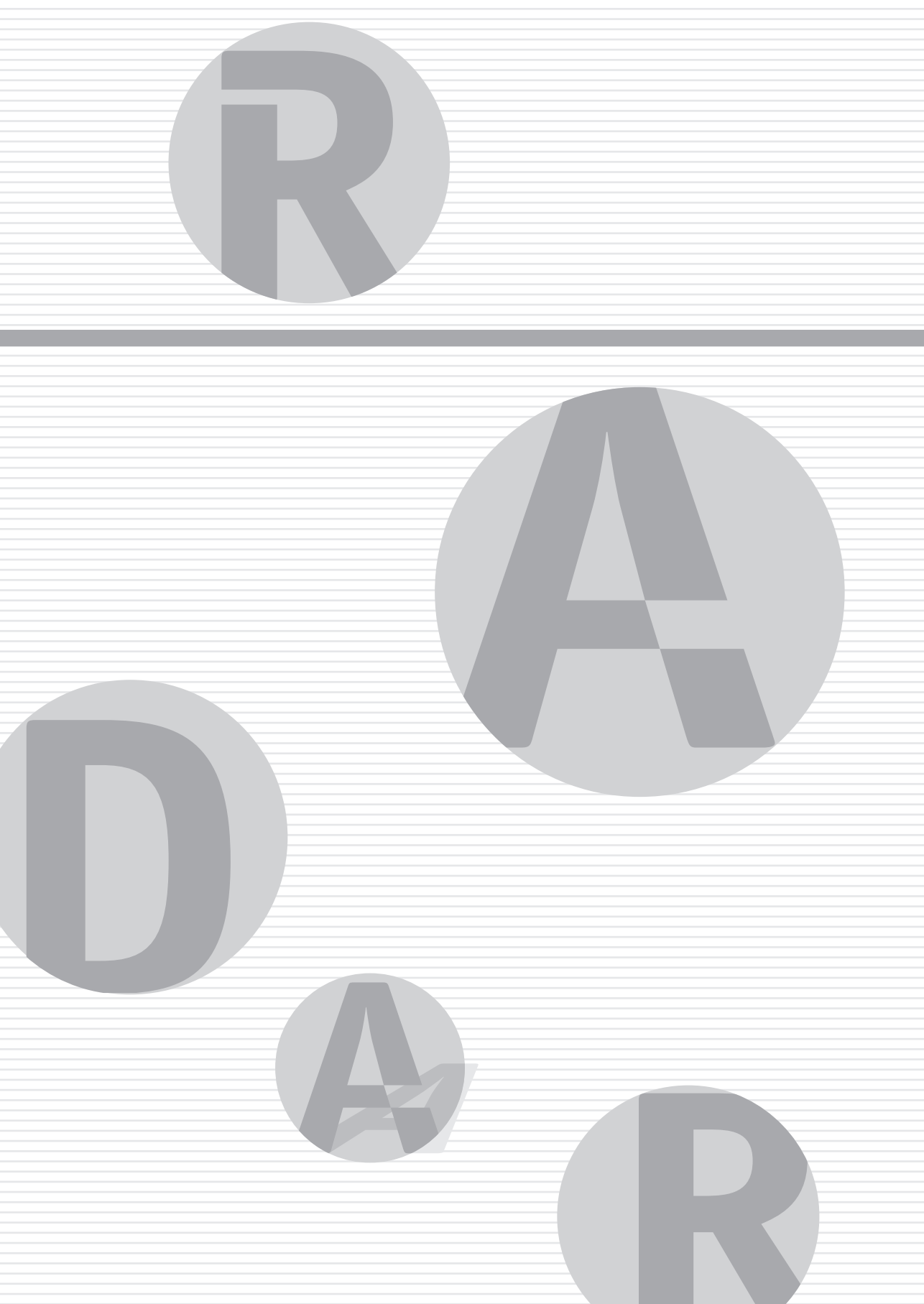
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Chapter 2

A Randomized Double-Blind Study of Atomoxetine Versus Placebo for Attention-Deficit/Hyperactivity Disorder Symptoms in Children With Autism Spectrum Disorder

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Abstract

Objective: The efficacy of atomoxetine as treatment of symptoms of attention deficit/hyperactivity disorder (ADHD) in patients with autism spectrum disorder (ASD) has not been established. **Method:** In this study, 97 patients aged 6-17 years with ADHD and ASD were randomly assigned to double-blind treatment with 1.2 mg/kg/day atomoxetine or placebo for 8 weeks. Primary endpoint was the ADHD Rating Scale (ADHD-RS), secondary endpoints the Clinical Global Impression of ADHD-Improvement (CGI-I) and the Conners Teacher Rating Scale-Revised: Short Form (CTRS-R:S). **Results:** Baseline mean ADHD-RS scores for atomoxetine versus placebo were 40.7 and 38.6; after 8 weeks, mixed-effect model repeated measure means were 31.6 [95% confidence interval 29.2 to 33.9] and 38.3 [36.0 to 40.6]), respectively, with a difference in least square means of –6.7 (–10.0 to –3.4; $p<0.001$). The CTRS-R:S Hyperactivity subscore also improved significantly for atomoxetine compared with placebo, but not the other CTRS-R:S subscores. However, there were not significantly more patients on atomoxetine (20.9%) who improved much or very much according to the CGI-I than on placebo (8.7%; $p=0.14$). Adverse events (mostly nausea, decrease in appetite, fatigue, and early morning awakening) were reported in 81.3% of atomoxetine patients and 65.3% of placebo patients ($p>0.1$). There were no serious adverse events. **Conclusions:** Atomoxetine moderately improved ADHD symptoms in patients with ASD and was generally well tolerated. Adverse events in this study were similar to those in other studies with ADHD patients without ASD.

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

The study was sponsored by Eli Lilly. Data analyses were performed by Alexander Schacht, PhD and Sireesha Pamulapati, PhD, both employees of Eli Lilly. The paper was written by the primary authors in alignment with Eli Lilly.

Introduction

The presence of symptoms of attention deficit/hyperactivity disorder (ADHD) in children with an autism spectrum disorder (ASD) is a serious clinical problem and frequently complicates these children's therapeutic management.[1] ASDs form a continuum of developmental disorders characterized by profound impairments in social relatedness, verbal and nonverbal communication skills, and stereotyped behaviors, with frequent presence of hyperactivity, self-injurious behavior, aggression towards others, and intolerance of change. Although the current version of the Diagnostic and Statistical Manual of Mental Disorders (fourth edition, text revised; DSM-IV-TR) formally precludes a diagnosis of ADHD in patients with ASD, a wealth of recent clinical and population-based studies have pointed to the relevance of ADHD in ASD.[2,3] Studies have also highlighted that ADHD symptoms can be reliably distinguished in the context of ASD.[2,3]

Appropriate medication in patients with ASD with ADHD symptoms might enhance the child's ability to benefit from educational and behavior modification interventions.[2] However, while the literature is full of studies on the efficacy of medications for ADHD,[4] hardly any studies directed at ADHD symptoms in children with ASD have been reported.

The effects of psychostimulants in children with ASD appeared to be lower compared to children with ADHD only, and the population with ASD may be more vulnerable to side-effects of psychostimulants, as suggested by a publicly sponsored double-blind, placebo-controlled multicenter trial of methylphenidate.[5]

Other commonly used agents in the treatment of ASD include antipsychotic medication such as risperidone and aripiprazole and the alpha-2 agonist guanfacine. Effects of risperidone for the treatment of severe irritability in children with ASD have been demonstrated in randomized controlled trials both in the short term as well as after several months of treatment.[6,7] Aripiprazole was shown to be efficacious and well tolerated in 8-week short-term treatment of severe irritability in children with ASD in two placebo-controlled studies.[8,9] Although antipsychotics may reduce overactivity, they do not appear to have robust effects on distractibility, inattention, or learning, even though we were able to show that risperidone had a beneficial effect after several months of treatment in enhancing divided attention in children with ASD.[10] Furthermore, risperidone may expose children to risks of significant long-term metabolic side-effects, such as weight gain.[11] Guanfacine has not been investigated in a randomized controlled trial in children with ASD. A retrospective open-label study seems to indicate some potential on reducing hyperactivity and attention problems, albeit with frequently occurring sedation.[12]

Atomoxetine, a noradrenergic reuptake inhibitor, is a newer approved medicine for the treatment of ADHD symptoms. It has been found to be superior to placebo in treating

ADHD symptoms in numerous randomized controlled trials and to be well-tolerated.[6,13-15] Currently, only three small open-label studies have reported on the possible effectiveness of atomoxetine in reducing ADHD symptoms in children and adolescents with ASD,[16-18] with promising results. Only one small-scale, double-blind, placebo-controlled crossover study of atomoxetine in 16 children and adolescents with ASD have been published.[19] Atomoxetine was reported to be superior to placebo on the primary outcome, the hyperactivity subscale of the Aberrant Behavior Checklist (p=0.043, effect size d=0.90). Upper gastrointestinal symptoms were the most common adverse events. All 16 patients on atomoxetine experienced mild upset stomach or nausea/vomiting versus five on placebo. Another common adverse event was fatigue, reported by 12 patients on atomoxetine versus 7 on placebo. Concomitant psychotropic medication was allowed in this study.[19]

The primary objective of this study was to test the hypothesis that atomoxetine would be superior to placebo in the treatment of symptoms of ADHD in patients with ASD as rated by the investigator-administered ADHD-RS.[20] Secondary objectives were to assess the effects of atomoxetine versus placebo on overall change of ADHD as indexed by the Clinical Global Impression scale rated by the investigator and on ADHD symptoms at school rated by the teacher. A further secondary objective was to assess the safety and tolerability of atomoxetine compared to placebo.

Our hypothesis was that atomoxetine would be superior to placebo on the clinician-based ADHD rating scale (ADHD-RS)[20] and would be well tolerated in children and adolescents with ASD.

Method

Study participants

Candidates for inclusion in the study were children and adolescents between 6 and 17 years with a clinical diagnosis of ASD and concomitant ADHD symptoms, who had been referred to one of nine participating Dutch child and adolescent psychiatry centers; six university centers (Amsterdam, Groningen, Leiden, Maastricht, Nijmegen, and Utrecht) and three nonuniversity centers (The Hague, Hoorn, and Oosterhout). Study candidates could also be recruited from other mental health institutions.

For inclusion in the study children had to have a confirmed diagnosis of ASD and to have concomitant ADHD symptoms according to our study criteria, plus an intelligence quotient (IQ) of at least 60 on a Wechsler Intelligence Scale (60 being an important limit for special education in the Netherlands). ASD diagnoses were confirmed through clinical assessment by certified child and adolescent psychiatrists (except in Oosterhout where

this was done by a certified child neurologist) and had to be corroborated by algorithm cut-off scores on the Autism Diagnostic Interview Revised; ADI-R;[21] that is, children had to have at least two ADI-R subscale scores above the cutoff, i.e., above 10 on the social interaction subscale, above 8 for verbal subjects and 7 for nonverbal subjects on the communication and language subscale, and/or above 3 on the restricted and repetitive behaviors subscale, thus operationalizing the whole range of ASD. To ensure diagnostic consistency across sites, all ADI-R assessments were done by raters who had been trained in using and interpreting the ADI-R by an accredited trainer. Study criteria of ADHD symptoms were in accordance with DSM-IV-TR criteria A through D for any subtype of ADHD, corroborated by scores of at least 1.5 standard deviations above the age norm for children's diagnostic subtype using published norms for the parent-based ADHD-RS.[22] ADHD study criteria assessment was done by a child and adolescent psychiatrist (or child neurologist) and was based on information of parents and teachers, a developmental history, and an interview with the child. Despite the formal preclusion of the DSM-IV-TR, diagnosing ADHD in children with ASD is now becoming an accepted practice.[5] Actually, removal of ASD from the excluders for a diagnosis of ADHD is now being considered in DSM V (see www.dsm5.org).

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

Exclusion criteria included a weight of less than 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.

Study interventions

Patients were randomized in a 1:1 ratio to receive either placebo or atomoxetine. Both atomoxetine and placebo were titrated in three weeks to a fixed once-daily dose of 1.2 mg/kg/day (first week: 0.5 mg/kg/day; second week: 0.8 mg/kg/day; third week 1.2 mg/kg/day). Atomoxetine and placebo were available as capsules and identical in appearance. Atomoxetine capsules contained 5, 10, 20, 25, or 40 mg. In order to preserve the blinding, all doses were given in two capsules which had to be taken together in the morning. Participating patients who started a psychoactive medication other than the study drug, a structured psychotherapy, or inpatient treatment had to discontinue study participation.

Study outcomes

The primary efficacy measure was change from baseline after 8 weeks of double-blind, placebo-controlled treatment on the total score of the investigator-administered ADHD-RS.[22] This DSM-IV based rating scale contains 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) and assesses symptom severity over the past week. 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. We obtained ADHD-RS ratings at baseline, after 5, and after 8 weeks of treatment.

Secondary outcome measures included the Clinical Global Impressions of ADHD-Improvement (CGI-ADHD-I), also assessed at baseline, after 5 and after 8 weeks; and the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S),[23] obtained at baseline and after 8 weeks. The CGI-ADHD-I[24] measures the total improvement (or worsening) of a patient's ADHD symptoms from the beginning of treatment, regardless of whether or not improvement (or worsening) is thought to be due entirely to drug treatment. Change is rated on a 7-point scale (1=very much improved; 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse). We classified ratings of 1 and 2 as improved and all other ratings as not improved. The CTRS-R:S is a 28-item questionnaire to be completed by the child's teacher to assess problem behaviors related to ADHD in the school setting. It includes subscales on oppositional behavior, hyperactivity, cognitive problems/inattention, and an ADHD index.

Safety was assessed by the same clinician who did the clinical ratings through open-ended questioning for adverse events by telephone after 1 and 2 weeks of treatment, and in person after 5 and 8 weeks of treatment. These were classified by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and judged to be related to the study drug or not. A serious adverse event was defined as death, life threatening, disability, or hospitalization. Adverse events that first occurred or worsened after study treatment started were defined as treatment-emergent adverse events.

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

Sample size

The initial assumption was that the improvement on the ADHD-RS would be approximately 7.0 points in the atomoxetine group and approximately 1.2 points in the placebo group, based on prior atomoxetine studies for children with ASD.[16,17] With a presumed standard deviation of 9 points, 43 patients were needed in each group (n=86) to achieve a power of 80%, using a two-sided significance level of 5%. Taking into account a drop-out rate of 15%, a total sample size of 100 patients was determined.

Randomization

Independent pharmacists dispensed either placebo or atomoxetine capsules according to a computer-generated randomization list. All study personnel and participants were blinded to treatment assignment for the duration of the study. The code was not revealed to the researchers until data collection for the study had been fully completed. The study statisticians were also blinded until completion of the analyses. Thus, maximum allocation concealment has been achieved.

Statistical methods

Efficacy and safety analyses were conducted on the full analysis set which, following the intent-to-treat principle, included all randomized patients receiving at least one dose of the study drug. Changes from baseline of the primary efficacy measure were compared between groups using mixed models for repeated measure (MMRM) and treatment comparisons for secondary efficacy were analyzed using analysis of covariance (ANCOVA) imputing missing values based on last observation carried forward (LOCF). Change from baseline was investigated by analyzing scale scores of atomoxetine and placebo-treatment-group patients at the end of the double-blind period while controlling for their baseline scores. The MMRM model included fixed effects for treatment, visit, treatment-by-visit interaction, and baseline value of the respective score. An unstructured covariance matrix was used and only in case of nonconvergence, an autoregressive covariance structure was applied. ANCOVA based on LOCF was done as supportive analysis. ANCOVA included fixed effects for treatment group and baseline score.

The CGI-ADHD-I was analyzed using Fisher's exact test. This scale was dichotomized combining very much and much improved versus all else. Unfortunately, CGI-ADHD-I ratings of drop outs at their last visits were not available; therefore, analyses of the CGI-ADHD-I could not follow the LOCF principle; instead, these were solely based on those patients who had completed the protocol.

Adverse events were analyzed as treatment-emergent adverse events and coded according to MedDRA. Post hoc, comparisons between groups were done using Fisher's exact test.

Results

Flow of participants

The CONSORT diagram (Figure 1) displays the flow of participants through the study. Three of the 97 randomized patients had erroneously been included in the study due to deviations from the inclusion and exclusion criteria. One child did not have an intelligence

quotient of at least 60. This child had a nonverbal intelligence quotient above 60, but was not testable with regard to his verbal intelligence quotient. Two other children with a clinical diagnosis of ASD did not meet algorithm cut-off scores on the ADI-R. There were no further deviations from the study as planned. Participants were enrolled from October 2006 to March 2008. One site did not recruit any patients.

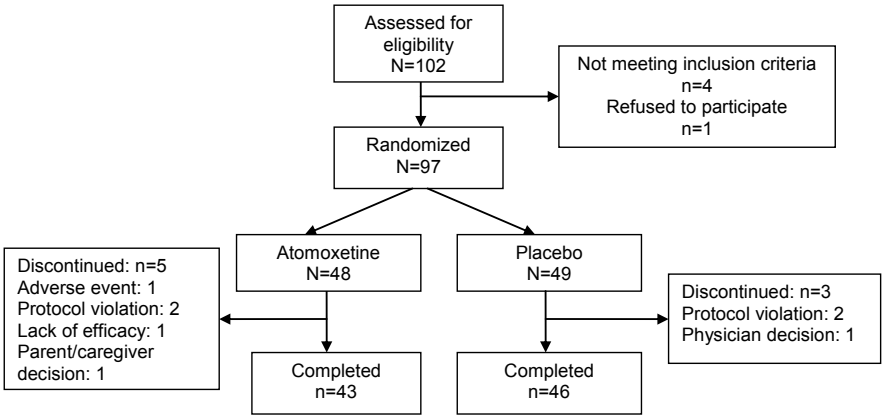

Figure 1. Flow diagram of a trial of atomoxetine versus placebo in children and adolescents with autism spectrum disorder and attention deficit/hyperactivity disorder symptoms

Number of participants

Following the intent-to-treat principle, the analyses were based on all patients who were randomly assigned, including the three patients who did not meet full inclusion criteria. As stated in the flow diagram (figure 1), 5 of 48 patients randomized to atomoxetine and 3 of 49 patients randomized to placebo discontinued for a variety of reasons.

Baseline demographic and clinical characteristics of both groups

The baseline characteristics of participants were similar between treatment groups (Table 1).

Characteristic	Atomoxetine N=48	Placebo N=49
Mean age in years (SD), range	9.9 (2.7), 6-16	10.0 (2.9), 6-17
Male sex, n (%)	42 (87.5%)	41 (83.7%)
Race		
White, n (%)	48 (100%)	48 (98%)
African, n (%)	0 (0%)	1 (2.0%)
Mean overall Wechsler IQ, (SD), range[a]	91.0 (16.4), 65-132	94.6 (17.7), 61-138
Mean CGI-ADHD-S, (SD), range	5.0 (0.74), 3-7	5.1 (0.90), 3-7
ASD diagnosis		
Autistic disorder,[b] n (%)	26 (54.2%)	32 (65.3%)
Asperger's disorder,[b] n (%)	3 (6.3%)	2 (4.1%)
PDDNOS,[b] n (%)	18 (37.5%)	14 (28.6%)
No ASD,[b] n (%)	1 (2.1%)	1 (2.0%)
No previous psychopharmacological treatment for ADHD, n (%)	18 (37.5)	18 (36.7)

Table 1. Baseline characteristics of participants in a trial of atomoxetine versus placebo in children and adolescents with ASD and ADHD symptoms

[a]In two children, total IQ was not available. One child (randomized to atomoxetine) had a nonverbal IQ above 60, but was not testable with regard to his verbal IQ and another child (randomized to placebo) had widely differing nonverbal and verbal IQs (of 55 and 85, respectively), therefore a total IQ could not be validly determined.

[b]Based on autism diagnostic interview-revised

Abbreviations: SD=standard deviation, 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, IQ=intelligence quotient

Summary of results

After 8 weeks of treatment, the ADHD-RS total and subscale scores had improved significantly more in the atomoxetine than in the placebo group, as shown by the results of the MMRM analysis (Table 2); the ADHD-RS total change (SD) from baseline for the atomoxetine group versus placebo group was –8.2 (8.8) and –1.2 (7.3), respectively. In addition, after 8 weeks of treatment, the mean (SD) ADHD-RS total score was lower in the atomoxetine group compared with the placebo group (atomoxetine: 32.3 [11.0] and placebo 37.3 [9.6]). The LOCF ANCOVA analysis also showed consistent results in that the atomoxetine group had lower ADHD-RS estimated least squares (LS) means compared with placebo after 8 weeks of treatment. Between-treatment differences in LS means of ADHD-RS subscores reached significance based both on MMRM and LOCF (Table 2).

	Atomoxetine (n=48)	Placebo (n=49)	Atomoxetine-placebo[a]	p value[b]
Mean score at baseline (SD), range				
ADHD-RS total score	40.7 (7.5), 28-54	38.6 (8.4), 20-54		
ADHD-RS inattention subscore	20.7 (3.9), 12-27	20.6 (4.6), 5-27		
ADHD-RS hyperactivity-impulsivity subscore	20.0 (5.3), 8-27	17.9 (6.1), 7-27		
LS mean at endpoint (95% CI) based on MMRM				
ADHD-RS total score	31.6 (29.2-33.9)	38.3 (36.0-40.6)	-6.7 (-10.0 – -3.4)	<0.001
ADHD-RS inattention subscore	17.2 (15.9-18.4)	19.9 (18.7-21.1)	-2.7 (-4.5 – -1.0)	0.003
ADHD-RS hyperactivity-impulsivity subscore	14.5 (13.0-15.9)	18.4 (17.0-19.7)	-3.9 (-5.9 – -1.9)	<0.001
LS mean at endpoint (95% CI) based on LOCF ANCOVA				
ADHD-RS total score	31.2 (28.9-33.6)	38.3 (36.0-40.5)	-7.0 (-10.3 – -3.7)	<0.001
ADHD-RS inattention subscore	17.0 (15.7-18.3)	19.9 (18.6-21.1)	-2.8 (-4.6 – -1.0)	0.002
ADHD-RS hyperactivity-impulsivity subscore	14.2 (12.8-15.7)	18.4 (17.0-19.7)	-4.1 (-6.1 – -2.1)	0.001
CGI-ADHD-I scores at endpoint, n (%)				
Very much improved	0 (0%)	1 (2.2%)		
Much improved	9 (20.9%)	3 (6.5%)		
Minimally improved	12 (27.9%)	6 (13.0%)		
No change	16 (37.2%)	30 (65.2%)		
Minimally worse	4 (9.3%)	3 (6.5%)		
Much worse	2 (4.7%)	3 (6.5%)		
Very much worse	0 (0%)	0 (0%)		

Table 2. Summary of ADHD-RS-scores (using MMRM and LOCF ANCOVA) and CGI-ADHD-I scores in a trial of atomoxetine versus placebo in children and adolescents with ASD and ADHD symptoms

[a]Difference in LS means between atomoxetine and placebo

[b]Main treatment effect for MMRM and treatment effect for ANCOVA, respectively

Abbreviations: MMRM=mixed models for repeated measurements, LOCF=last observation carried forward, ANCOVA=analysis of covariance, LS=least square, ASD=autism spectrum disorder, ADHD=attention deficit/hyperactivity disorder, ADHD-RS=ADHD-rating scale, SD=standard deviation, CI=confidence interval, CGI-ADHD-I=Clinical Global Impressions of ADHD-Improvement

The CGI-ADHD-I indicated improvement in 9 of 43 patients (20.9%) allocated to atomoxetine versus 4 of 46 (8.7%) patients receiving placebo, a between-group difference that did not reach significance (Fisher's exact test; p=0.14) (Table 2).

The CTRS-R:S showed a mean change from baseline that was significantly greater in patients allocated to atomoxetine than in patients receiving placebo only in the Hyperactivity domain (p=0.024). Between-group differences in CTRS-R:S Cognitive Problems/Inattention and Oppositional subscale change scores did not reach significance, while differences in CTRS-R:S ADHD Index change scores approached significance (Table 3).

	Atomoxetine (n=48)	Placebo (n=49)	Atomoxetine-placebo[a]	p value[b]
Mean score at baseline (SD), range				
CTRS-R:S oppositional score	4.1 (3.5), 0-12	3.6 (3.5), 0-13		
CTRS-R:S hyperactivity score	8.8 (5.5), 0-20	8.2 (5.1), 1-19		
CTRS-R:S cognitive/attention score	6.8 (4.5), 0-15	4.8 (3.7), 0-14		
CTRS-R:S ADHD score	18.5 (9.3), 0-34	18.1 (7.5), 2-31		
LS mean at endpoint (95% CI) based on LOCF ANCOVA				
CTRS-R:S oppositional score	3.2 (2.3-4.0)	3.7 (2.9 -4.6)	-0.6 (-1.8 – 0.7)	0.37
CTRS-R:S hyperactivity score	6.8 (5.5-8.0)	8.8 (7.6-10.0)	-2.0 (-3.7 – -0.3)	0.024
CTRS-R:S cognitive/attention score	5.1 (4.4-5.8)	5.8 (5.1-6.5)	-0.7 (-1.7 – 0.3)	0.18
CTRS-R:S ADHD score	15.1 (13.0-17.2)	17.8 (15.7-19.8)	-2.7 (-5.6 – 0.3)	0.077

Table 3. LOCF ANCOVA analyses for change from baseline in CTRS-R:S scores in a trial of atomoxetine versus placebo in children and adolescents with autism spectrum disorder and ADHD symptoms

[a]Difference in LS means between atomoxetine and placebo

[b]Main treatment effect

Abbreviations: LOCF=last observation carried forward, ANCOVA=analysis of covariance, CTRS-RS=Conners Teacher Rating Scale-Revised: Short Form, LS=least square, CI=confidence interval, CTRS-R:S=Conners' teacher rating scale-revised: short form, ADHD=attention deficit/hyperactivity disorder

Adverse events

None of the patients had a serious adverse event. One patient in the atomoxetine group discontinued due to an adverse event (fatigue) versus none in the placebo group. In the atomoxetine group 39 of 48 patients (81.3%) reported at least one adverse event, versus 32 of 49 (65.3%) in the placebo group (Fisher's test p value: 0.11); 35 of 48

subjects (72.9%) reported adverse events which were possibly drug related, versus 27 of 49 (55.1%) in the placebo group. Table 4 shows the number of treatment-emergent adverse events occurring in 5% or more of patients, by MedDRA preferred term.

Type of AE[b]	Occurrence of AE in atomoxetine group, n=48, n (%)	Occurrence of AE in placebo group, n=49, n (%)	Fisher's test p value for between-group differences
Nausea	14 (29.2%)	4 (8.2%)	0.009
Decreased appetite	13 (27.1%)	3 (6.1%)	0.006
Headache	12 (25.0%)	9 (18.4%)	0.47
Fatigue	11 (22.9%)	4 (8.2%)	0.053
Upper abdominal pain	9 (18.8%)	3 (6.1%)	0.071
Vomiting	7 (14.6%)	5 (10.2%)	0.55
Early morning awakening	5 (10.4%)	0 (0.0%)	0.027
Abdominal pain	4 (8.3%)	3 (6.1%)	0.72
Dizziness	3 (6.3%)	1 (2.0%)	0.36
Influenza	3 (6.3%)	0 (0.0%)	0.12
Initial insomnia	3 (6.3%)	5 (10.2%)	0.72
Myalgia	3 (6.3%)	0 (0.0%)	0.12
Aggression	2 (4.2%)	3 (6.1%)	0.99
Diarrhea	1 (2.1%)	3 (6.1%)	0.62
Psychomotor hyperactivity	1 (2.1%)	4 (8.2%)	0.36
Pyrexia	0 (0.0%)	3 (6.1%)	0.24

Table 4. Summary of treatment-emergent adverse events occurring in 5% or more of children and adolescents with autism spectrum disorder and attention deficit/hyperactivity disordersymptoms randomized to either atomoxetine or placebo[a]

[a]Assessed by open-ended questioning for adverse events by telephone after 1 and 2 weeks of treatment, and in person after 5 and 8 weeks of treatment.

[b]Adverse events classified according to Medical Dictionary for Regulatory Activities Preferred Term

Abbreviation: AE=Adverse events

Discussion

This is the first adequately powered placebo-controlled study examining the efficacy and safety of atomoxetine for symptoms of ADHD in children with ASD. Our findings indicate that atomoxetine is superior to placebo after a treatment period of 8 weeks and generally well tolerated. There were no serious adverse events. Only one patient in

the atomoxetine group discontinued because of a (nonserious) adverse event. Reported adverse events in this study population are already listed. With atomoxetine, however, the frequency tended to be somewhat higher than described in the atomoxetine summary of product characteristics, especially regarding occurrence of fatigue, nausea, decreased appetite, and early morning awakenings.[25]

Atomoxetine appeared to have positive effects on both attention deficit and hyperactivity-impulsivity symptoms according to clinician-based ratings, with clearly larger improvements on hyperactivity-impulsivity. Teacher ratings on the CTRS-R:S also indicated larger benefits on hyperactive symptoms, with only trend-level improvements in cognitive/inattention symptoms. This is in agreement with the earlier 6 weeks placebo controlled trial that also found clinician-rated improvement in hyperactivity symptoms, but only trend-level improvement in inattentive symptoms in children with ASD.[19] These findings indicate that atomoxetine has a more pronounced effect on hyperactivity than on inattention. This is in contrast with the effects of atomoxetine in children with typical ADHD, where similar effect sizes on inattention and hyperactivity have been reported.[26,27] It is unlikely, given prior studies with atomoxetine,[28] that the effects of atomoxetine on ADHD symptoms were mediated by or confounded by effects on anxiety symptoms.

The magnitude of the effect of atomoxetine appears to be somewhat smaller in children with ASD than what has generally been reported in children with typical ADHD. In our study, the mean change from baseline in the ADHD-RS was 8.2 points, whereas this change in children with typical ADHD has repeatedly been found to be in the range of 13-19 points, even though baseline ratings of ADHD have been similar.[25-28]

The relatively lesser effect of atomoxetine in children with ASD is also indicated by the small proportion (around 20%) of children on atomoxetine who improved much or very much as rated by the CGI-ADHD-I. This proportion is in contrast to smaller-scale or open-label studies of atomoxetine for ADHD symptoms in children with ASD that found much or very much improvement in the range of 43%[17] to 75%.[18] In our study, the proportion of patients on atomoxetine who clearly improved did not differ significantly from the placebo group. However, our study was not powered for the comparison of the proportion of much or very much improved children and results need to be interpreted under this limitation. The overall mediocre CGI results may be due to the CGI reflecting an overall change of ADHD status in the context of a complex comorbid condition of ASD and ADHD, whereas the ADHD symptoms score changes are more specific.This highlights the difficulty of treating ADHD symptoms in children with ASD.

The magnitude of the effect of methylphenidate has also been found to be smaller and the frequency of adverse events higher in children with ASD compared to children with typical ADHD.[5] Thus, the situation with regard to atomoxetine is similar in this respect. However, we currently lack direct comparisons between psychostimulants and

atomoxetine regarding efficacy and tolerability. Moreover, comparison of effects is hampered by the fact that the one available methylphenidate study with adequate sample size in children with ASD used different outcome measures.

Our study has some limitations. First, for the diagnosis of ADHD, we relied on routine clinical procedures and did not use a formal diagnostic interview. ASD diagnoses had to be corroborated by algorithm cut-off scores on the ADI-R, but we allowed inclusion of children who did not meet ADI-R cut-off scores on the social interaction domain, in deviation from DSM-IV-TR criteria for Pervasive Developmental Disorder Not Otherwise Specified. Moreover, the study may have been too short for atomoxetine to reach its full effect. For example, Montoya et al[31] found continuing improvement up to 12 weeks in ADHD symptoms in treatment-naïve children and adolescents with ADHD (without ASD). A longer placebo-controlled period could also clarify whether rates of adverse events would wane over time. Furthermore, the reliability of the teacher ratings may have been limited by some measurement error due to missing teacher reports and transition of children to new classes with different teachers. However, it has been shown that parent ratings are as sensitive as teacher ratings in medication trials.[27,32] Another limitation may have been the fact that we did not use standardized rating scales to assess adverse events, but used open-ended questioning. We may thus have missed adverse events, such as dysthymia. Finally, our study sample had relatively few adolescents, female subjects, and children with IQs in the lower range, making findings possibly less generalizable for these groups.

In conclusion, our findings suggest that atomoxetine is efficacious and safe in an 8-week treatment period for ADHD symptoms in patients with ASD. Improvement in both ADHD symptom domains may be achieved, with expected gains in hyperactivity-impulsivity being somewhat larger. More controlled double-blind and longer-duration studies are needed to replicate our study findings.

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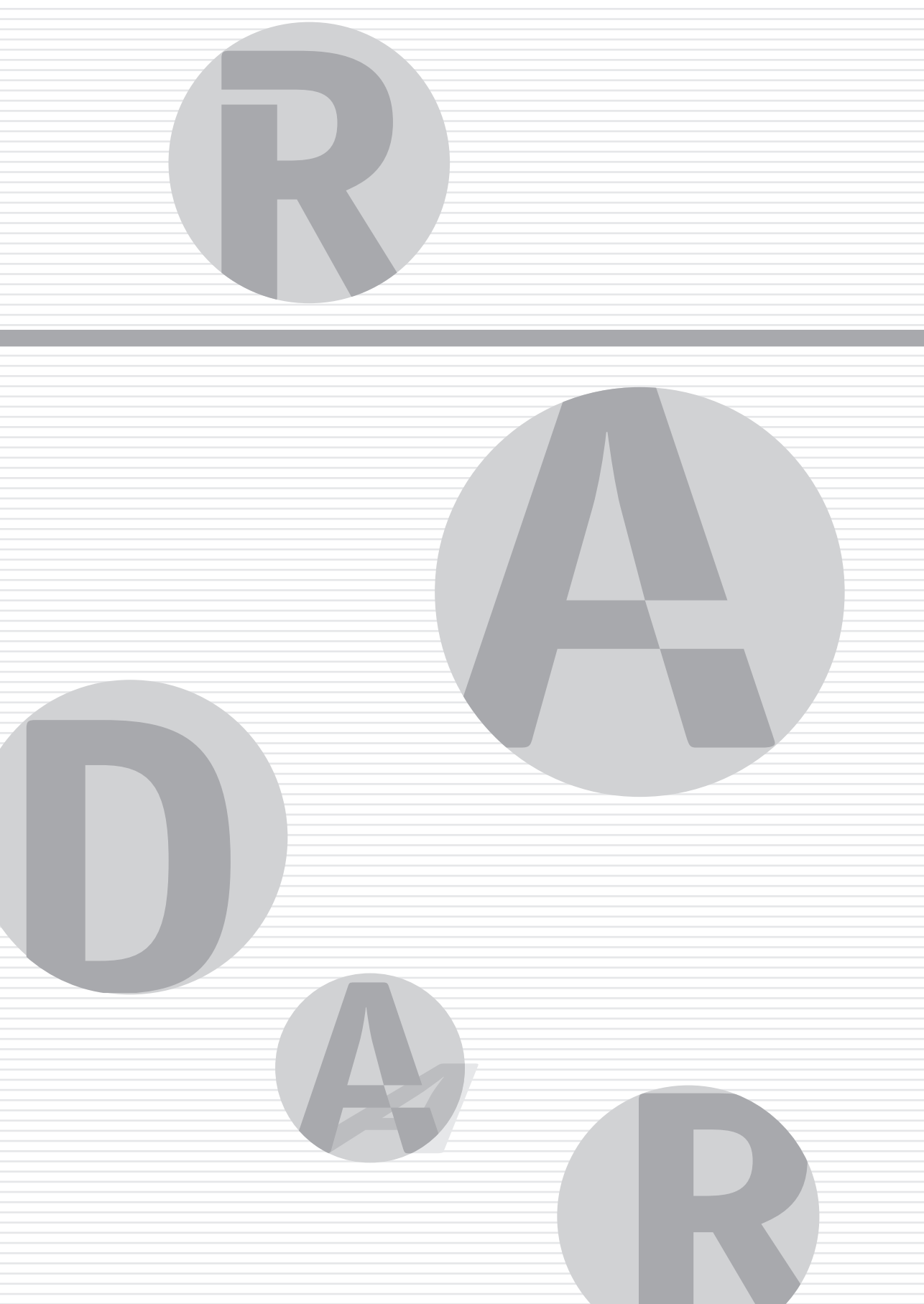
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Chapter 3

Long Term Treatment with Atomoxetine for ADHD Symptoms in Children with ASD: an open label extension study

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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. **Method:** In this study, 88 patients aged 6-17 years 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 with ASD, while adverse events tend to subside. Future studies investigating the long term efficacy of atomoxetine in children with ASD should be randomized and placebo-controlled.

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

This study was funded by Eli Lilly and company. Data analyses were done by Myriam Harfterkamp and Pieter J. Hoekstra. The paper has been fully written by the authors.

Clinical Significance

The presence of symptoms of attention deficit/hyperactivity disorder (ADHD) in children with an autism spectrum disorder (ASD) is a serious clinical problem and frequently complicates these children's therapeutic management. Appropriate medication in patients with ASD with ADHD symptoms might enhance the child's ability to benefit from educational and behavior modification interventions. However, while the literature is full of studies on the efficacy of medications for ADHD, hardly any studies directed at ADHD symptoms in children with ASD have been reported. Our study suggests that atomoxetine is effective on ADHD symptoms in children with ASD and is well tolerated, with ongoing improvement during continued treatment.

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 weeks trial in 97 children and adolescents with an autism spectrum disorder (ASD) and concomitant ADHD symptoms and demonstrated superior efficacy of atomoxetine compared to 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 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 thirteen clinical trials (six double-blinded placebo-controlled and seven open label studies) showed a gradual clinical response up to three 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 until 12 months (Kratochvil et al. 2006). The long-term effects of atomoxetine in children and adolescents with typical ADHD were 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 $\geq$ 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 eight weeks of treatment would diminish over time in children with ASD and concomitant ADHD.

We hypothesized that continued treatment with atomoxetine for ADHD symptoms in children with ASD beyond eight weeks would be associated with further decrease of clinician-rated ADHD symptoms, whilst 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).

Material 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 with both ASD and ADHD who had participated in an 8 week randomized double blind multi-center 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 eight week trial.

Inclusion and exclusion criteria

For inclusion in the study, children had to be between 6 and 17 years, to have an intelligence quotient of at least 60 on a Wechsler Intelligence Scale (60 being an important limit for special education in the Netherlands), and to have a clinical diagnosis of both ASD and ADHD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders fourth edition, 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 cut-off, i.e., above 10 on the social interaction subscale, above 8 on the communication and language subscale (for nonverbal subjects this had to be above 7), and/or above 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 centres could recruit patients for the study, six university centres (Amsterdam, Groningen, Leiden, Maastricht, Nijmegen, and Utrecht) and three non-university centres (The Hague, Hoorn, and Oosterhout).

Exclusion criteria included a weight of less than 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 in-patient 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 in-patient treatment had to discontinue study participation.

Both parents and children of 12 years and older had to give written informed consent, while 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 children's treatment allocation, dosing of atomoxetine in all children started at 0.5 mg/kg/day for one 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 three 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 20 weeks.

Measurements

As efficacy measure, we used the investigator-rated ADHD-rating scale based on parents report (ADHD-RS), 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 child 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, life threatening, 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 originally allocated to atomoxetine, we did a repeated measures analysis of variance (ANOVA) of 8, 13, 16, and 28 weeks of treatment with atomoxetine, followed by paired-sample T-tests of 8 versus 13, 13 versus 16, and 16 versus 28 weeks of treatment.

For all patients, we compared the frequency of adverse events as reported in the first 8 weeks of treatment with atomoxetine (for the group originally allocated to placebo, these were the first 8 weeks of the open label extension part) versus the frequency of those reported after 8 weeks of initial treatment, by using the McNemar test.

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 children 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 children 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 children, the mixed model analyses showed a significant average decrease per week on the total ADHD-RS of 0.27 (95% C.I.0.48 to 0.06; p=0.01), on the ADHD-RS inattention subscale of 0.14 (95% C.I.0.25 to 0.03; p=0.01) and on the ADHD-RS hyperactivity-impulsivity subscale of 0.13 (95% C.I.0.25 to 0.001; p=0.05).

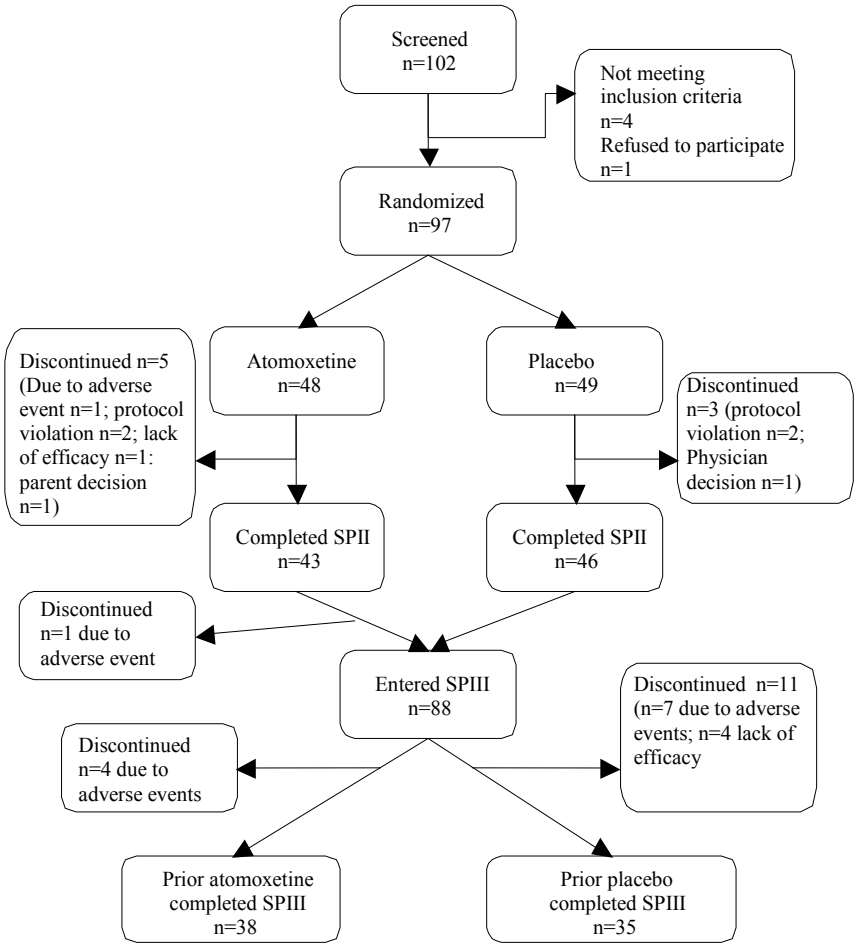

Figure 1. Flow diagram of a trial of atomoxetine versus placebo followed by an open label extension period in children and adolescents with ASD and ADHD symptoms

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 for; 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 for; 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=0-27), paired-sample T-test t= 6.8; df=87; p <0.001 for. Thus, these results indicate improvement on continued treatment with atomoxetine after an initial treatment period of 8 weeks. Finally, for the group originally allocated to atomoxetine, the total ADHD-RS as well as the ADHD-RS inattention and hyperactivity-impulsivity subscale decreased significantly between the time points of 8, 13, 16, and 28 weeks of total treatment (repeated measures ANOVA F=298, p<0.001 for the total ADHD-RS; F=269, p<0.001 for the inattention ADHD-RS; and F=221, p<0.001 for the hyperactive-impulsive ADHD-RS). Results of paired-sample T-tests indicated significant decreases in the total and inattention and hyperactivity-impulsivity ADHD-RS between most consecutive time points (see table 2).

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

Table 1. Baseline characteristics of participants with ASD and ADHD in a 20 week open label extension treatment with atomoxetine following an 8 week randomized double blind trial of atomoxetine versus placebo

Abbreviations: 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

[1]Based on Autism Diagnostic Interview-Revised

[2]These children had erroneously been included in the study

Total treatment length with atomoxetine	Total ADHD-RS Mean (SD) Paired samples T test statistics[1]	Inattention ADHD-RS subscale Mean (SD) Paired samples T test statistics[1]	Hyperactivity-Impulsivity ADHD-RS subscale Mean (SD) Paired samples T test statistics[1]
Baseline	40.3 (7.1)	20.6 (3.9)	19.7 (5.0)
8 weeks	32.4 (11.1) t=5.9; p <0.001	16.9 (6.1) t=5.1; p<0.001	15.5 (6.5 t=5.4; p<0.001
13 weeks	29.2 (11.2) t=3.5; p=0.001	15.1 (6.2) t=3.5; p=0.001	14.1 (6.2) t=2.7; p=0.01
16 weeks	27.7 (12.4) t=1.8; p=0.075	14.6 (6.7) t=1.2; p=0.245	13.1 (6.8) t=1.9; p=0.068
28 weeks	24.9 (12.2) t=2.5; p=0.015	13.0 (6.6) t=2.6; p=0.011	11.8 (6.7) t=1.9; p=0.062

Table 2. Results of paired-sample T-tests of ADHD-RS total and inattention and hyperactivity-impulsivity subscale scores between consecutive time points for the group originally allocated to atomoxetine[2]

Abbreviations:
ADHD=attention deficit/hyperactivity disorder
ADHD-RS=ADHD Rating Scale
SD=standard deviation

[1]versus previous assessment

[2]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 children who started the 20 weeks open label extension period, 11 children stopped due to adverse events (4 originally allocated to atomoxetine and 7 originally allocated to placebo). Two children, both originally allocated to atomoxetine, were hospitalized (appendicitis and right pneumothorax) but there was no relation with the study drug and these two children completed the whole study. No serious adverse events occurred during the whole study period.

Table 3 shows the frequency of adverse events reported during the first 8 weeks of treatment compared to those reported in the subsequent 12 or 20 weeks of treatment. Of note, both fatigue and nausea had diminished in frequency upon continued treatment.

Adverse Event	Reported during first 8 weeks of treatment with atomoxetine n (%)[1]	Reported during subsequent 12 or 20 weeks of treatment n (%)	Significance level[2]
Abdominal Pain	6 (6.8%)	2 (2.3%)	0.22
Abdominal Pain Upper	11 (12.5%)	7 (8.0%)	0.42
Decreased Appetite	16 (18.2%)	8 (9.1%)	0.096
Early Morning Awakening	5 (5.7%)	1 (1.1%)	0.22
Fatigue	16 (18.2%)	6 (6.8%)	0.041
Headache	18 (20.5%)	13 (14.8%)	0.38
Influenza	5 (5.7%)	2 (2.3%)	0.38
Initial Insomnia	6 (6.8%)	6 (6.8)	1
Nausea	12 (13.6%)	1 (1.1%)	0.003
Vomiting	6 (6.8%)	5 (5.7%)	1

Table 3. Adverse Events reported in the first 8 weeks of treatment with atomoxetine compared to continued treatment of 12 or 20 weeks

[1]Only those occurring in at least 5% of patients during the first 8 weeks of treatment.

[2]Proportion 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 with ASD in an open label extension period of 20 weeks after an 8 week placebo controlled trial. While results of the first 8 weeks period indicated better efficacy of atomoxetine compared to 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 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 thus 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 due to 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 six month double blind trial of treatment with atomoxetine in adults with ADHD (n=491), where a discontinuation of 17.2% due to 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 towards 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 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 with ASD should be randomized and placebo-controlled.

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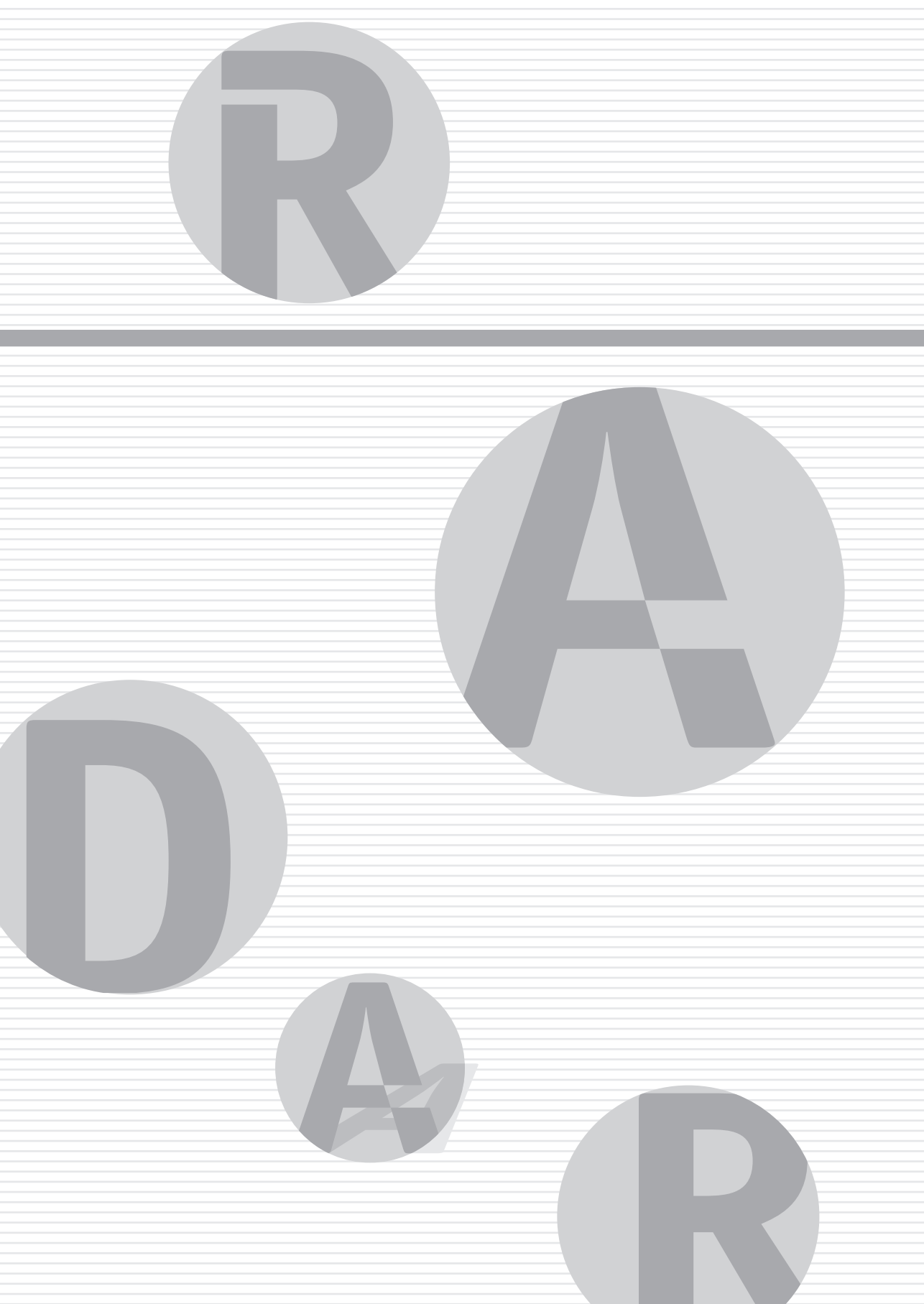
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Chapter 4

A Randomized, Double-blind Comparison of Atomoxetine and Placebo on Response Inhibition and Interference Control in Children and Adolescents with Autism Spectrum Disorder and comorbid Attention-Deficit/ Hyperactivity Disorder symptoms

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To the editors

The clinical descriptions of Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are quite distinctive, still both disorders frequently co-occur: about 20 to 50% of patients with ADHD meet criteria for ASD and about 30 to 80% of patients with ASD meet criteria for ADHD.[1] It has now been recognized that both disorders share a substantial proportion of etiological risk factors,[2] and the DSM-5 draft includes the possibility of a comorbid diagnosis. This has given impulse to several clinical trials investigating the effectiveness of pharmacological treatment such as methylphenidate for ADHD symptoms in ASD-patients.[3,4] Overall, it was concluded that the benefits seen from methylphenidate were smaller and side effects were more frequently reported amongst comorbid patients as opposed to pure ADHD patients. Therefore, recent reviews on the efficacy and tolerability of medical treatment options for ADHD-like symptoms in individuals with ASD suggest that in addition to methylphenidate, atomoxetine may be a reasonable choice to target ADHD symptoms in ASD.[5] We previously reported on the effect of atomoxetine on ADHD symptom severity in children with both ASD and ADHD using a double-blind placebo-controlled design in 97 children.[6] Results indicated that atomoxetine improved ADHD symptoms in children with ASD according to both parent and clinician-based ratings and was generally well tolerated.

Knowledge of the efficacy of medical treatment on cognitive deficits associated with ADHD provides more insight into the working mechanisms of a pharmacological agent. For the mixed dopamine and norepinephrine re-uptake inhibitor methylphenidate, research has consistently shown its improvement of the neural mechanisms of inhibitory control in ADHD-patients.[7] In contrast, for the selective norepinephrine re-uptake inhibitor atomoxetine, findings are somewhat contrasting. This may partially be explained by the broad definition of inhibitory control; it encompasses amongst others response inhibition and interference control. Response inhibition is best described as an output-process reflecting stimulus selection, whereas interference control is input-dependent, reflecting response organization. These aspects do not necessarily correlate with each other[8], hence a selective norepinephrine re-uptake inhibitor (atomoxetine) and a mixed dopamine and norepinephrine re-uptake inhibitor (methylphenidate) may influence distinct mechanisms of inhibitory control. Change in the neural mechanisms of inhibitory control as a result of atomoxetine treatment has thus far not been studied in patients suffering from both ASD and ADHD symptoms. Our aims were to examine 1) whether atomoxetine improved two forms of inhibitory control (response inhibition and interference control), and 2) whether ADHD symptom improvement[6] was mediated by improvements in inhibitory control.

Exact screening procedures and study design for the double-blind placebo controlled phase have been described previously.[6] Of the 89 out of 97 children who completed the 8 week double-blind placebo controlled phase, one child decided to discontinue in the open label treatment period. 88 started the open-label phase; 42 previously on atomoxetine and 46 previously on placebo. Fifteen children withdrew from this phase of the study because of adverse events or lack of efficacy, resulting in 73 patients completing the open-label phase. No differences between the atomoxetine and placebo group were found regarding sex (87.5 % and 83.7% male, respectively), age (*M* (*SD*); 10.5 (2.7) and 10.4 (2.9), respectively), IQ (*M* (*SD*); 91.0 (16.4) and 94.6 (17.7) respectively) and ADHD symptom severity (see Table 1). The first (neuro-)psychological measures were administered at the start (T1) and at the end (T2) of the double-blind placebo controlled phase. Next, the open label phase had a duration of 20 weeks and at the end of this period, the final (neuro-)psychological measures were administered (T3). During this open-label phase both groups were treated with atomoxetine, titrated identically as in the double-blind placebo controlled phase, i.e. both study personnel and participants remained blinded to treatment assignment for the complete duration of the study.

Test–retest reliability and validity of both inhibitory control measures are satisfactory and have been described and illustrated elsewhere.[9] The Go-No Go task was administered to measure the response inhibition of pre-potent responses. In this task, 24 Go signals, in response to which the subjects had to press a key, were randomly mixed with 24 No Go signals, to which responses had to be suppressed. The valid response window was 200 ms to 2300 ms post stimulus onset. Primary outcome measure was the proportion of false alarms after No Go signals. Secondary outcome measures were the proportion of missed Go signals, the response time and response time variability of correct responses. The Focused Attention task was administered to measure interference control, i.e., the degree of distractibility by irrelevant information. In this task, 20 relevant target trials, in response to which the subject had to press a 'yes-button', were randomly mixed with both 10 non-target trials and 10 trials with foils (interference trials) to which the subject had to respond by pressing a 'no-button'. In the target trials, the target was shown at a vertical position, whereas in the non-target trials the stimulus was absent. In the foil-trials, the stimulus was presented in a horizontal position, which participants were required to ignore. The valid response window was 200 ms to 6000 ms post stimulus onset. Primary outcome measure was the proportion of false alarms on the interference trials. Secondary outcome measures were the proportion of false alarms on the non-target trials, the proportion of relevant targets missed, response time and response time variability of correct responses. ADHD symptom improvement was measured using the ADHD Rating Scale (ADHD-RS)[10] and the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S),[11] these outcomes were reported previously.[6]

Correlations between congruent measures of both tasks (e.g. reaction time variables of both tasks) were calculated at T1, T2 and T3 to examine the (in)dependence of both inhibitory control domains. Last observation carried forward (LOCF) analyses were conducted, with the requirement of having at least a neuropsychological assessment at T1. In total, 94/97 had a T1 assessment of the response inhibition task and 95/97 children of the interference control task. First, to examine the effect of atomoxetine on both forms of inhibitory control, two analyses were conducted: (a) groups were compared using only the blinded measurements prior (T1) and post treatment (T2); and (b) change after first treatment was analyzed combining change during the blind phase (T2-T1) for the atomoxetine group and change during the open label phase (T3-T2) for the placebo group. Second, inhibitory control measures that significantly changed in response to atomoxetine treatment were used to examine the possible mediating effects of inhibitory control on the change in ADHD symptoms. Parametric (reaction time and reaction time variability) and non-parametric (proportion of false alarms and misses) correlations were calculated between Δ inhibitory control (T2-T1 for the blind group and T3-T2 for the open label group) and Δ ADHD symptoms (T2-T1 for the blind group and T3-T2 for the open label group), in which negative scores reflected improvement (less ADHD symptoms and less erroneous and faster performance as a results of treatment). Group characteristics for measures of inhibitory control and ADHD symptom severity are presented in Table 1.

Both primary outcome measures did not correlate significantly (r = .15, p = .17). Except for the proportion of misses in both tasks (r = .38, p < .001), none of the other cognitive or behavioral outcome measures correlated significantly. A significant treatment effect was found on the primary outcome measure of response inhibition according to both the blind phase analyses as well as change after first treatment analyses. In contrast, the primary outcome measure of interference control did not improve after atomoxetine treatment in the blind or open label phase. A significant treatment effect was found on ADHD symptoms as assessed by the ADHD-RS during the blind and open label phases. For the CTRS-R:S, significant ADHD symptom improvements were only reported according to change after first treatment analyses. Correlations between ADHD symptoms, error measures and response time (variability) in both response inhibition and interference control were non-significant (r's between .00 and .13 for parents and between .02 and .16 for teachers, all p's > .10, and between .04 - .16 for parents and -.15 - .02 for teachers, all p's > .10, respectively).

	T1: Baseline[a]		T2: End of double blind phase		T3: End of open label phase		Group comparison blind phase[b]	Change after first treatment[c]
	ATX M (SD)	Placebo M (SD)	ATX M (SD)	Placebo M (SD)	ATX M (SD)	Formerly placebo M (SD)	LOCF F/Wald-χ^2, p	LOCF M [95% CI]
RESPONSE INHIBITION	n=47/48	n=47/49	n=47/48	n=47/49	n=42/48	n=46/49		
- Proportion false alarms	.07 (.10)	.06 (.08)	.04 (.05)	.08 (.11)	.06 (.07)	.06 (.08)	**3.64, .05**	**-0.02 [-0.04 - -0.001]**
- Proportion misses	.02 (.06)	.02 (.05)	.03 (.06)	.02 (.05)	.01 (.04)	.02 (.04)	**3.83, .05**	0.00 [-0.01 – 0.01]
- Response time	532.7 (144.9)	485.0 (120.7)	525.7 (132.8)	490.5 (104.6)	501.7 (134.8)	491.4 (117.4)	0.07, .80	-2.30 [-17.17 – 12.57]
- Response time variability	125.1 (64.0)	120.0 (77.2)	144.2 (86.5)	137.7 (79.6)	133.2 (72.2)	118.3 (69.4)	0.00, .99	-1.51 [-15.53 – 12.51]
INTERFERENCE CONTROL	n=47/48	n=48/49	n=43/48	n=47/49	n=42/48	n=46/49		
- Proportion false alarms on interference trials	.06 (.10)	.03 (.05)	.04 (.07)	.03 (.07)	.06 (.10)	.05 (.08)	0.10, .75	0.00 [-0.02 – 0.02]
- Proportion false alarms on non-target trials	.13 (.16)	.10 (.12)	.10 (.13)	.13 (.14)	.11 (.14)	.12 (.13)	0.95, .33	-0.02 [-0.05 – 0.01]
- Proportion misses	.05 (.06)	.06 (.09)	.10 (.11)	.05 (.06)	.06 (.06)	.07 (.11)	**4.88, .03**	0.03 [0.01 – 0.05]
- Response time	1081.4 (419.7)	1045.4 (480.7)	985.7 (465.8)	1012.9 (462.3)	931.9 (389.5)	948.1 (458.9)	0.88, .35	**-47.22 [-129.60 - -18.85]**
- Response time variability	454.1 (299.6)	459.9 (334.6)	356.0 (263.9)	387.6 (290.3)	372.6 (326.2)	383.2 (276.1)	0.30, .58	-45.57 [-94.91 – 3.77]
ADHD SYMPTOM SEVERITY	n=43/48	n=47/49	n=42/48	n=47/49	n=39/48	n=42/49		
- ADHD-RS[10]	40.7 (7.5)	38.6 (8.4)	32.6 (11.0)	37.6 (9.8)	27.5 (12.0)	25.3 (12.2)	**13.83, <.001**	**-9.39 [-11.52 - -7.26]**
- CTRS-R:S[11]	18.5 (9.3)	18.1 (7.5)	15.5 (9.8)	17.6 (9.0)	13.4 (8.7)	14.9 (7.3)	3.39, .07	**-2.27 [3.70 - -0.87]**

Table 1. Means and standard deviations of ADHD measures and inhibitory control measures before atomoxetine treatment (T1), after double blind placebo controlled treatment (T2) and after an open label extension (T3).

ATX = Atomoxetine, LOCF = Last observation carried forward. ADHD-RS[10]= ADHD Rating Scale, CTRS-R:S[11] = Conners' Teacher Rating Scale-Revised: Short Form.

94/97 children had a T1 assessment of the Response inhibition task and 95/97 children of the Interference control task

[a] For 2 children the response inhibition measurement and for 3 children the interference control measurement of T0 was used for T1 because of missing data at T1.

[b] Difference between atomoxetine and placebo post treatment, corrected for pre-treatment. ANCOVAs were used for reaction time (variability) with group as factor, the pre-treatment (T1) as covariate and post-treatment (T2) as dependent measure. Negative binominal models were used for error measures, since these data showed substantial underdispersion, with group as factor, the pre-treatment (T1) as covariate and post-treatment (T2) as dependent measure.

[c] Change after first treatment using one-sample t-test (response time (variability)) or non-parametric tests (error measures) against a test-value of 0 (no change after treatment): double blind phase for the atomoxetine group (T2-T1), open label phase for the placebo group (T3-T2).

Discussion

This is the first double blind, placebo controlled study to demonstrate selective beneficial effects of atomoxetine on response inhibition but not interference control in children with both ASD and ADHD symptoms. The finding that atomoxetine improves response inhibition is in line with the majority of previous studies documenting response inhibition in children with ADHD.[12] Our study adds to these findings by illustrating that response inhibition can also be improved in patients with ASD and comorbid ADHD symptoms, tentatively suggesting that the origins of response inhibition problems in these comorbid patients may be of similar nature as those observed in pure ADHD patients. This hypothesis is further supported by the improvements of ADHD symptoms as a result of treatment with atomoxetine in this patient group[6] as well as in previous (mostly open-label) studies.[13,14] All in all, atomoxetine appears to improve both response inhibition problems as well as ADHD symptoms in patients with ASD and ADHD, suggesting this to be an effective method of treatment in these patients. In contrast, the effect of atomoxetine on interference control was absent, which runs counter to some previous studies examining the effect of atomoxetine on interference control in ADHD patients,[15] but is in line with others.[16] The differential effect of atomoxetine on response inhibition on the one hand and interference control on the other hand, is not surprising given that these functions do not necessarily correlate with each other, which was the case in our study as well as previous studies.[8] The neural substrates of response inhibition (an output-process reflecting stimulus selection), and interference control (an input-dependent process reflecting response organization) in ADHD are not yet fully understood. It has been suggested that alteration in the neural basis of response inhibition

and interference control in childhood ADHD are characterized by distinct patterns of functional abnormality.[17] The functional activity associated with response inhibition in ADHD is a decreased activation of the prefrontal and striatal brain regions (including the inferior frontal gyrus and cingulate cortex),[18,19] whereas for interference control, a reduced activitity of the frontal-striatal cortex (including the cingulate cortex) as well as parietal cortex has been reported in ADHD.[17,20] These findings suggest that atomoxetine mainly exert its effects on the prefrontal cortex underlying response inhibition, and not on the parietal brain regions also required for interference control in patients with ASD and ADHD symptoms. In other words, the enhanced frontal-striatal functioning via the selective norepinephrine re-uptake inhibitor may be sufficient to improve response inhibition, but insufficient to improve interference suppression because parietal-temporal contributions are necessary.[20] Further functional imaging studies are required to confirm or refute this hypothesis.

An intriguing finding reported here was the lack of association between ADHD symptom improvement and improvements in inhibitory control, which may suggest that distinct pathogenic pathways play a role in clinical symptoms and cognitive dysfunctions. The absence/presence of such a relationship is a relatively neglected topic in studies reporting on pharmaceutical effects on cognitive and symptom data, yet is of great relevance in understanding the mechanisms of action of a pharmacological agent. It has been suggested that cognitive deficits in psychiatric disorders may act as epiphenomena: related to the same etiological underpinnings as the disease symptoms, but not mediating between both. This may suggest that predicting or monitoring treatment response using cognitive tests may not be of clinical utility, at least in the case of atomoxetine treatment in children with ASD and ADHD symptoms using inhibitory control tasks.

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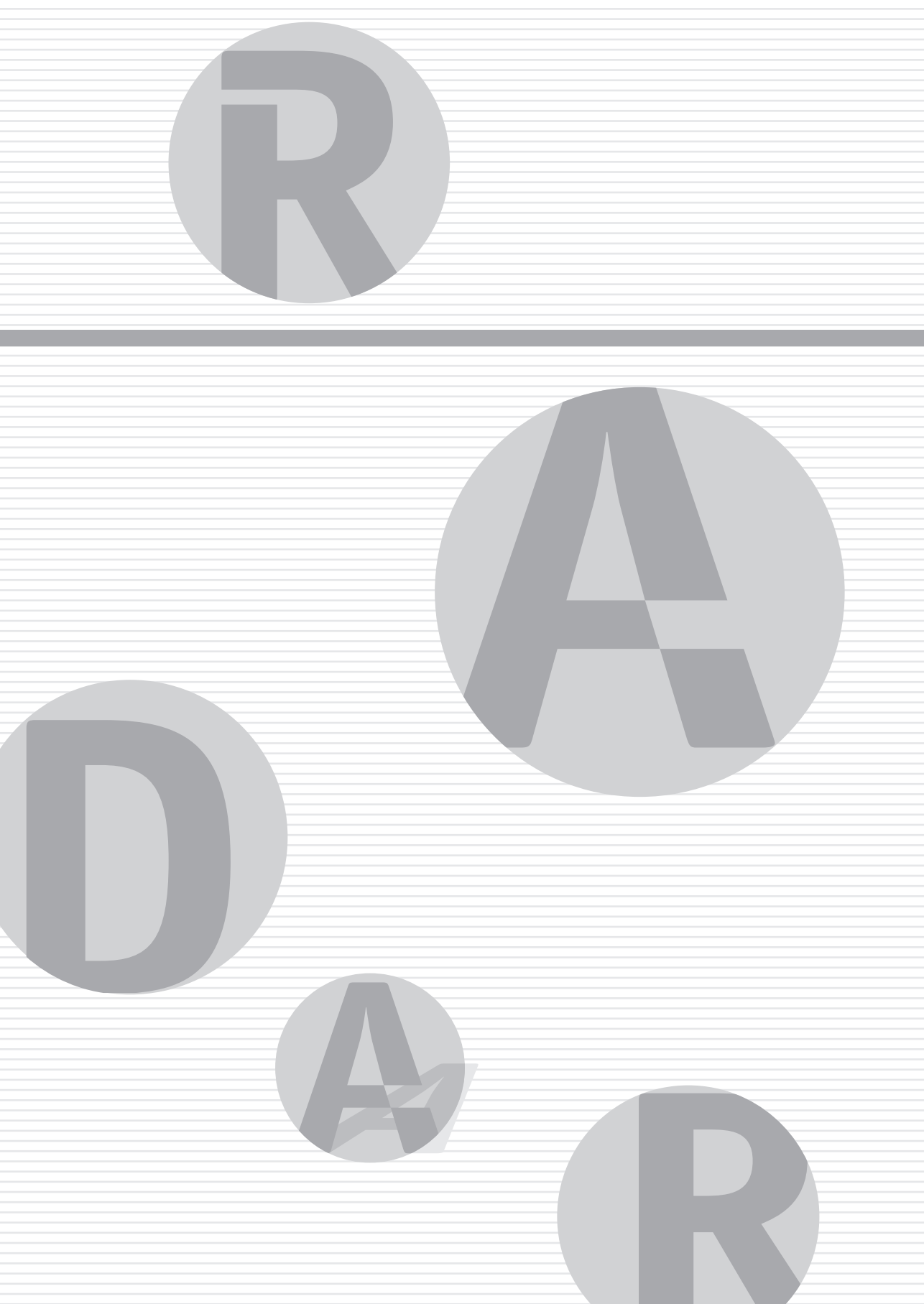
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Chapter 5

Atomoxetine in Autism Spectrum Disorder: no effects on social functioning, some benefits on stereotyped behaviors, inappropriate speech, and fear of change

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Abstract

Objectives: To investigate the short term treatment effects of atomoxetine on Autism Spectrum Disorder (ASD) symptoms in children with both ASD and Attention-Deficit/Hyperactivity Disorder (ADHD). **Methods:** 97 patients aged 6-17 years with ASD and ADHD were treated with 1.2 mg/kg/day atomoxetine in an 8 week double-blind placebo-controlled period. Here, we investigated effects on two parent-based secondary outcome measures, the Aberrant Behavior Checklist (ABC) and the Children's Social Behavior Questionnaire (CSBQ). **Results:** After 8 weeks of double-blind treatment, atomoxetine administration was associated with significant treatment effects on the ABC subscales Hyperactivity, Inappropriate Speech, and Stereotypic Behavior and on the CSBQ subscale Fear for Changes. **Conclusion:** Our study results indicate no beneficial effects of atomoxetine on social functioning. However, atomoxetine may ameliorate restricted and stereotyped behaviors and communication.

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

This study was sponsored by Eli Lilly. Data analyses were done by Myriam Harfterkamp and Pieter J. Hoekstra. The paper has been written by the authors.

Clinical Significance

Autism Spectrum Disorders (ASD) are a continuum of developmental disorders characterized by impairments in social interaction, verbal and nonverbal communication skills, and stereotyped behaviors, with various frequently co-occurring problems such as symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD), self-injurious behavior, aggression, mood problems, sensory differences, sleep dysfunction, and intolerance of change. While we previously found effects of atomoxetine on ADHD symptoms in children with ASD and co-occurring symptoms of ADHD, the current analyses suggest no beneficial effects of atomoxetine on social functioning. These results are in line with existing studies showing that social functioning is not very responsive to currently available psychopharmacological treatment that have been tested in ASD to date. Still, we did find some indication of benefits through atomoxetine on stereotyped behaviors, inappropriate speech, fear of change, and on hyperactivity.

Introduction

Autism Spectrum Disorders (ASD) are a continuum of developmental disorders characterized by impairments in social interaction, verbal and nonverbal communication skills, and stereotyped behaviors, often with various co-morbid features such as Attention Deficit Hyperactivity Disorder (ADHD) symptoms, self-injurious behavior, aggression, mood problems, sensory differences, sleep dysfunction, and intolerance of change (Leyfer et al. 2006).

There is currently no curative treatment for ASD. The overall treatment goal is to improve the child's functioning, ideally by reducing impairments in social interaction, communication, and repetitive behaviors. Behavioral interventions can improve children's language abilities, play and cognitive skills, and social functioning and may reduce maladaptive behavior (Dawson and Burner 2011). Psychotropic medication may also improve children's functioning and allow children with ASD to benefit more optimally from educational interventions (Anagnostou and Hansen 2011 and Huffman et al. 2011).

The three classes of medication most extensively studied in ASD clinical trials are atypical neuroleptics, psychostimulants, and selective serotonin reuptake inhibitors (SSRI's). Current evidence indicates efficacy of atypical neuroleptics for ameliorating irritability and repetitive behaviors in ASD, with the strongest level of empirical support for risperidone and aripiprazole (McDougle et al. 2005, Marcus et al. 2009 and Marcus et al. 2011). Further, positive effects of methylphenidate in children with ASD and hyperactivity have been observed on social communication and self-regulation (Jahromi et al. 2009). Finally, a well-designed and powered study indicated ineffectiveness of citalopram, suggesting no clear place for SSRI's in the treatment of children with ASD (King et al. 2009).

Atomoxetine, a noradrenergic reuptake inhibitor registered for the treatment of ADHD, may be effective in ameliorating ADHD symptoms in children with ASD, as indicated by a number of small scale studies (Troost et al. 2006, Arnold et al. 2006, Posey et al. 2006, Jou et al. 2005) and by our placebo-controlled trial involving almost 100 subjects (Harfterkamp et al. 2012). Some of the smaller studies had also suggested improvements in core ASD symptoms and social functioning (Arnold et al. 2006 and Posey et al. 2006).

Our study in children with combined ASD and ADHD consisted of a first 8 week double-blind period of atomoxetine versus placebo followed by a 20 week open label continued treatment period and used the ADHD rating scale ADHD-RS as primary outcome measure (Faries et al. 2001). Here, we present the possible effects of atomoxetine on ASD symptoms as investigated in the placebo-controlled part of the study, measured by two parent-based secondary outcome measures, the Aberrant Behavior Checklist (ABC)

(Aman et al. 1985) and the Children's Social Behavior Questionnaire (CSBQ) (Hartman et al. 2006).

Method

Study participants

We provided detailed inclusion criteria previously (Harfterkamp et al. 2012). In brief, children had to be between 6 and 17 years, to have an intelligence quotient of at least 60, and to have a dual diagnosis of ASD and ADHD. ASD diagnosis was based on clinical assessment and had to be corroborated by at least two subscale scores on the Autism Diagnostic Interview Revised (ADI-R) above the cut-off (Rutter et al. 2003); ADHD diagnoses had to meet Diagnostic and Statistical Manual of Mental Disorders fourth edition, text revised (DSM-IV-TR) criteria A through D for ADHD any type. Nine Dutch child and adolescent psychiatry centers could recruit patients for the study, six university centers (Amsterdam, Groningen, Leiden, Maastricht, Nijmegen, and Utrecht) and three non-university centers (The Hague, Hoorn, and Oosterhout). Exclusion criteria included a weight of less than 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 in-patient treatment.

Both parents and children of 12 years and older had to give written informed consent, while younger children had to assent. The study had been approved by the national and local institutional review board committees. Participants were enrolled in the placebo-controlled study from October 2006 to March 2008.

Study interventions

Patients were randomized in a 1:1 ratio to receive either placebo or atomoxetine capsules titrated to a fixed once-daily dose of 1.2 mg/kg/day (first week: 0.5 mg/kg/day; second week: 0.8 mg/kg/day; then 1.2 mg/kg/day for 6 weeks).

Outcome measures

To rate changes in ASD symptoms we used two parent-based questionnaires, the ABC and the CSBQ, which were obtained at baseline and at the end of the study, i.e. after 8 weeks. The ABC is a 58-item scale which consists of five subscales, labeled Irritability (includes agitation, crying, and self-injurious behaviors, contains 15 items, e.g., screams inappropriately; aggressive to other children or adults; depressed mood); Lethargy/ Social Withdrawal (includes social withdrawal, has 16 items, e.g., seeks isolation from

others; does not try to communicate with words or gestures; fixed facial expression); Stereotypic Behavior (7 items, e.g., moves or rolls head repetitively; repetitive hand, body, or head movements); Hyperactivity (includes noncompliance, 16 items, e.g., impulsive [acts without thinking]; restless, unable to sit still; disobedient, difficult to control), and Inappropriate Speech (4 items, e.g., talks excessively; repetitive speech). The ABC was developed as a measure of treatment effects in patients with developmental disabilities. It has been used in drug research and other forms of clinical research and has been shown to be sensitive to the effects of psychotropic drugs (Troost et al. 2006, Aman et al. 1985 and Karabekiroglu and Aman 2009).

The CSBQ consists of 49 items covering a broad range of features typical for ASD, from subtle social, communication, and repetitive behavioral impairments seen in children with milder forms of ASD to more severe autistic-like features, with an emphasis on the former (Hartman et al. 2006). Items are rated on a three point likert-type fashion (i.e., 0= does not apply at all; 1= applies slightly or infrequently; 2= applies clearly or often). The CSBQ consists of a total scale and six subscales: Subscale 1 Behavior/emotions not optimally tuned to the social situation (11 items, e.g., does not know when to stop; goes on and on about things; makes a fuss over little things; makes a mountain of a mole-hill); Subscale 2 Reduced contact and social interest (12 items, e.g., has little or no need for contact with others; does not seek comfort when he/she is hurt or upset; lives in a world of his/her own); Subscale 3 Orientation problems in time, place, or activity (8 items, e.g., does things without realizing what stage of the activity he/she is; has no sense of time); Subscale 4 Difficulties in understanding social information (7 items, e.g., takes things literally; is exceptionally naïve); Subscale 5 Stereotyped behavior (8 items, e.g., is extremely pleased by certain movements and keeps doing them; is fascinated by certain colors, forms, or moving objects); and Subscale 6 Fear of and resistance to changes (3 items, e.g., panics in new situations or if change occurs). Multiple estimates of reliability and validity of the CSBQ were found to be good (Hartman et al. 2006, Luteijn et al. 2000, and Bildt de et al. 2009).

Data analysis

Analyses were conducted on the full data set which, following the intent-to-treat principle, included all randomized patients receiving at least one dose of the study drug. Changes from baseline to 8 weeks on the ABC subscales and the CSBQ total scale and subscales were analyzed using analysis of covariance (ANCOVA), imputing missing values based on last observation carried forward (LOCF). ANCOVA included fixed effects for treatment group and baseline score. We used a p value <0.05 to indicate statistical significance. In light of the relatively small sample size, we did not adjust the alpha level for multiple comparisons, to avoid false negative findings.

Results

Participants

Figure 1 shows the flow of the 97 participants through the study. The baseline demographic and clinical characteristics of participants were similar between the treatment groups in the double-blind treatment phase (table 1). As stated in the flow diagram, 5 of 48 children randomized to atomoxetine and 3 of 49 children randomized to placebo discontinued for a variety of reasons.

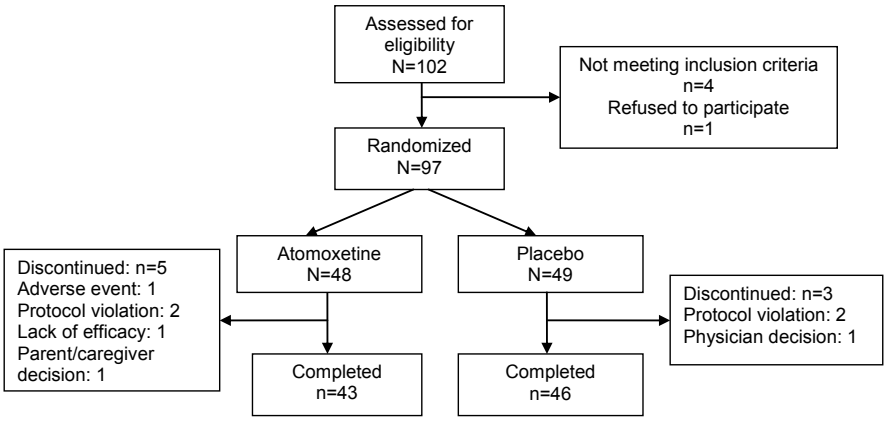

Figure 1. Flow diagram of a trial of atomoxetine versus placebo in children and adolescents with autism spectrum disorder and attention deficit/hyperactivity disorder symptoms

Characteristic	Atomoxetine n=48	Placebo n=49
Mean age, y, (SD), range	9.9 (2.7), 6-16	10.0 (2.9), 6-17
Male gender, n (%)	42 (87.5)	41 (83.7)
Mean overall IQ (Wechsler), (SD), range	91.0 (16.4), 65-132	94.6 (17.7), 61-138
No previous psychopharmacological treatment, n (%)	18 (37.5)	18 (36.7)
Autistic disorder[1], n (%)	26 (54.2)	32 (65.3)
All other ASDs[2], n (%)	22 (45.9)	17 (34.7)

Table 1. Baseline characteristics of participants in our 8 weeks trial of atomoxetine versus placebo in children and adolescents with ASD and ADHD symptoms

[1]Based on clinical diagnosis, corroborated by ADI-R
[2]Based on clinical diagnosis, corroborated by ADI-R, but two participants had a clinical diagnosis of ASD which was (in deviance with the protocol) not corroborated by ADI-R scores; one in each treatment group

Abbreviations: SD=standard deviation, ADI-R=autism diagnostic interview-Revised, ASD=autism spectrum disorder, IQ=intelligence quotient

Measure	Atomoxetine (n=48) Mean (SD) at baseline, LS mean after 8 weeks (95% CI)[1]	Placebo (n=49) Mean (SD) at baseline, LS mean after 8 weeks (95% CI)[1]	Cohen's d effect size for difference between atomoxetine and placebo[1]	Difference in LS means between atomoxetine and placebo (95% CI)[1]
ABC Irritability subscale	17.3 (9.1), 14.6 (12.7-16.4)	16.2 (9.5), 15.6 (13.8-17.3)	0.2	1.0 (-3.5 - 1.6) p=0.452
ABC Lethargy/ Social Withdrawal subscale	12.5 (8.4), 11.4 (9.9-13.0)	12.5 (8.0), 11.7 (10.1-13.2)	0.0	0.2 (-2.4 – 2.0) p=0.850
ABC Stereotypic Behavior subscale	6.5 (5.1), 3.0 (2.1-3.9)	4.1 (4.5), 4.6 (3.7-5.4)	0.5	1.6 (-2.8 - -0.3) p=0.014
ABC Hyperactivity subscale	28.4 (9.3), 21.2 (18.8-23.6)	25.4 (11.5), 25.6 (23.3-27.9)	0.6	4.4 (-7.8 - -1.1) p=0.010
ABC Inappropriate Speech subscale	4.7 (3.2), 3.7 (3.3-4.3)	4.6 (3.4), 4.5 (4.0-5.1)	0.4	0.9 (-1.7-0.0) p=0.045
CSBQ Total scale	53.6 (14.8), 46.2 (43.2-49.2)	53.1 (15.7), 50.1 (47.2-53.1)	0.4	3.9 (-8.1-0.3) p=0.069
CSBQ Not Tuned subscale	14.8 (4.8), 13.0 (12.0-14.0)	14.9 (5.3), 14.1 (13.2-15.1)	0.3	1.2 (-2.6-0.3) p=0.106
CSBQ Reduced Contact subscale	10.5 (5.5), 8.9 (8.0-9.8)	10.9 (4.4), 9.5 (8.6-10.4)	0.2	0.6 (-1.9-0.6) p=0.331
CSBQ Orientation Problems subscale	9.8 (2.7), 8.9 (8.2-9.7)	9.9 (3.5), 9.0 (8.3-9.8)	0.0	0.1 (-1.2-1.0) p=0.889
CSBQ Social Information subscale	9.4 (3.3), 8.7 (8.1-9.2)	9.6 (3.4), 9.3 (8.8-9.8)	0.3	0.6 (-1.4-0.1) p=0.110
CSBQ Stereotyped subscale	5.8 (4.0), 4.2 (3.4-4.9)	4.8 (3.7), 5.0 (4.3-5.7)	0.3	0.8 (-1.8-0.2) p=0.123
CSBQ Fear for Changes subscale	3.3 (1.9), 2.6 (2.3-3.0)	3.0 (1.9), 3.2 (2.8-3.5)	0.4	0.6 (-1.1-0.0) p=0.035

Table 2. Changes in ABC subscales and CSBQ total scale and subscale scores from baseline to 8 weeks of double-blind treatment with atomoxetine versus placebo.

[1]based on last observation carried forward ANCOVA
ABC=Aberrant Behavior Checklist
CSBQ=Children's Social Behavior Questionnaire
SD=Standard Deviation
LS=Least Square

Outcomes

After 8 weeks of double-blind treatment, the scores on the ABC subscales Hyperactivity, Inappropriate Speech, and Stereotypic Behavior and the CSBQ subscale Fear for Changes were significantly more lowered from baseline in the atomoxetine than in the

placebo group. None of the other ABC subscales and CSBQ total scale and subscales showed statistically significant different change scores from baseline to 8 weeks of treatment between atomoxetine and placebo (table 2).

Discussion

The present study investigated possible effects of atomoxetine on ASD symptoms in children with ASD and ADHD symptoms. We used parent-based secondary outcome measures (ABC and CSBQ) in an 8 week double-blind placebo-controlled trial. Overall, no treatment effects were observed on the hallmark ASD symptom domain of impairments in social interaction as indicated by lack of improvements on the CSBQ subscales Not Tuned, Reduced Contact, and Social Information.

Still, we observed some modest improvements in other ASD symptom domains. We found superior effects of atomoxetine on the ABC subscales Hyperactivity, Inappropriate Speech, and Stereotypic Behavior. Obviously, the effect on the ABC Hyperactivity subscale is directly related to improvements on ADHD symptoms, in line with our previously reported findings of superior effects of atomoxetine compared to placebo on the clinician based ADHD-RS (Harfterkamp et al. 2012). The other two ABC subscales contain items referring to communication and stereotyped behaviors. These ABC findings are largely in line with two earlier, small scale studies with atomoxetine in children with ASD. A small-scale double-blind placebo-controlled crossover study of clinically titrated atomoxetine and placebo, six weeks each, separated by 1-week wash out in 16 children and adolescents with ASD reported effects on the ABC subscales Hyperactivity and Lethargy/Social Withdrawal (Arnold et al. 2006). Another 8 week open label prospective study in 16 children with ASD showed effects of atomoxetine on the ABC subscales Hyperactivity, Stereotypic Behavior, Lethargy/Social Withdrawal, and Inappropriate Speech (Posey et al. 2006). It should be noted, however, that our finding of an overall change of around 20% on the 4-item ABC Inappropriate Speech subscale, while statistically significant, may not necessarily point to improvement in Inappropriate Speech per se, but could also be related to changes in ADHD symptoms (e.g., the ABC Inappropriate Speech item "talks excessively" could have improved due to decreased ADHD symptoms rather than a change in core features of ASD).

Fear for changes was the only CSBQ subscale on which atomoxetine had superior effects compared to placebo. This is in line with previous studies that had suggested possible effects of atomoxetine on anxiety, as found in children and adults with ADHD and an anxiety disorder (Geller et al. 2007 and Adler et al. 2009). However, better handling of changes may also indicate an effect of atomoxetine on ameliorating restrictive behavior,

in line with the positive effects of atomoxetine on the ABC Stereotypic Behavior subscale. It must be noted though, that the CSBQ Fear for changes subscale has only three items; with a decrease of around 20%, the improvement may not be clinically meaningful. Also, the lack of benefits on the Stereotypy CSBQ subscale does not substantiate the possible effects of atomoxetine on ameliorating stereotyped behaviors. While, we have no direct explanation for the differing results on the CSBQ subscale Stereotypy versus the ABC subscale Stereotypic Behavior, the lack of consistency most likely reflects differences in item content between these two subscales.

A number of limitations need to be acknowledged. Perhaps the most critical one has been the choice of rating scales to assess improvements on ASD symptoms. For this, we relied entirely on parent-ratings, without clinical assessment, observation, or use of teacher ratings. However, the ABC has become something of a gold standard for trials in this area. As a second limitation, it should be noted that the study had not been primarily powered to investigate improvements on ASD symptoms. It cannot be excluded that a larger sample size would still indicate effects of atomoxetine on social behavior, even when adjusting levels of significance for multiple comparisons.

In summary, our study indicates no beneficial effects of atomoxetine on social functioning, after 8 weeks of treatment. These results are in line with existing studies showing that social functioning is not very responsive to currently available psychopharmacological treatment that have been tested in ASD to date (Anagnostou and Hansen 2011 and Huffman et al. 2011). Still, we did find some indication of benefits through atomoxetine on stereotyped behaviors, inappropriate speech, and fear of change and on hyperactivity. The latter finding is in line with our previously reported improvements on ADHD symptoms (Harfterkamp et al. 2012 and Harfterkamp et al. 2013). These benefits may have children with ASD profit more from behavioral interventions, which should be investigated in future studies.

Conclusions

In summary, our study indicates no beneficial effects of atomoxetine on social functioning after 8 weeks of treatment. These results are in line with existing studies showing that social functioning is not very responsive to currently available psychopharmacological treatments that have been tested in ASD to date (Anagnostou and Hansen 2011; Huffman et al. 2011). Still, we did find some indication of beneficial effects of atomoxetine on stereotyped behaviors, inappropriate speech, and fear of change, and on hyperactivity. The latter finding is in line with our previously reported improvements in ADHD symptoms (Harfterkamp et al. 2012, 2013). These benefits may help children and adolescents with ASD to profit more from behavioral interventions, which should be investigated in future studies.

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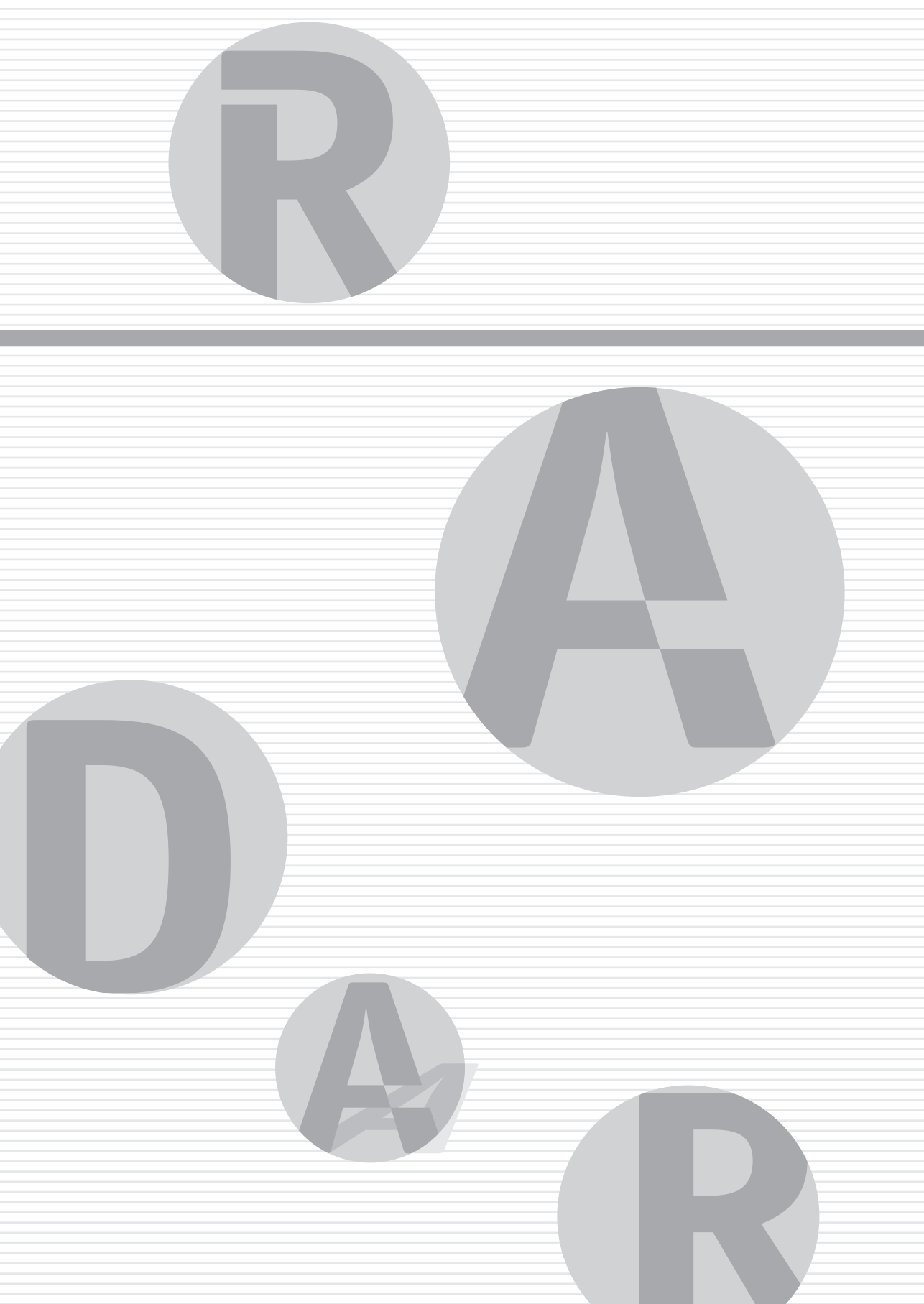
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Chapter 6

No evidence for predictors of response to atomoxetine treatment of Attention-Deficit/Hyperactivity Disorder symptoms in children and adolescents with Autism Spectrum Disorder

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To the editor

Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms are frequently observed in children and adolescents with an Autism Spectrum Disorder (ASD); about 30-80% of patients with ASD meet criteria for ADHD (Rommelse et al. 2010). The presence of ADHD in children and adolescents with ASD is a serious clinical problem; patients with such a dual diagnosis have more severe overall impairment which frequently complicates these patients therapeutic management (Holtmann et al. 2007; Gadow et al. 2006). Although a combination of these diagnoses were precluded by the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (text revision; DSM-IV-TR), the DSM-5 has now made it possible to classify both disorders at the same time.

Several small-scale, mostly open label studies (Posey et al. 2006; Jou et al. 2005; Arnold et al. 2006; Troost et all. 2006; Zeiner et al. 2011; Charnsil 2011; and Fernández-Jaén et al. 2013) have suggested that atomoxetine, a noradrenergic reuptake inhibitor, might be a promising treatment for ADHD symptoms in children and adolescents with ASD. We have confirmed these preliminary findings in a double-blind placebo-controlled trial followed by an open label extension period in children and adolescents with ASD and concomitant ADHD symptoms and demonstrated superior efficacy of atomoxetine compared to placebo, as rated by the investigator-administered ADHD-Rating Scale (ADHD-RS), with good tolerability (Harfterkamp et al. 2012). We also showed that continued treatment with atomoxetine up to a total treatment length of 28 weeks led to further improvement of ADHD symptoms in children with ASD and to a decrease of adverse events (Harfterkamp et al. 2013).

However, these group findings do not necessarily predict treatment response for an individual patient. From a clinical perspective it is worthwhile to know which patients with ASD and ADHD are most likely to have a good response to atomoxetine. A meta-analysis and meta-regression-analysis has evaluated the efficacy and safety of atomoxetine in children and adolescents with ADHD (without ASD) across nine randomized placebo-controlled trials (in total 1150 patients on atomoxetine) (Cheng et all. 2007). These analyses suggested that atomoxetine is more effective in patients with higher baseline ADHD symptom count, whereas male gender, presence of comorbid oppositional defiant disorder (ODD), and of ADHD hyperactive/impulsive type were associated with somewhat smaller symptom reductions. However, another large-scale (in total 618 patients treated with atomoxetine) pooled analysis of six industry sponsored U.S. randomized, double blind, placebo controlled atomoxetine trials ruled out baseline ADHD symptom count, male sex, ADHD type, race, previous stimulant use, presence of comorbid ODD, age, and *CYP2D6* genotype status as predictors of achieving a much improved clinical response (Newcorn et al. 2009). The only factor associated with much improved response was

having at least a minimal decrease of 25% on the ADHD-RS total score within the first 4 weeks of treatment (Newcorn et al. 2009). A subsequent retrospective analysis of five placebo-controlled atomoxetine trials (in total 562 patients on atomoxetine) confirmed that early changes in ADHD-RS items after 1 to 3 weeks treatment may reliably predict a beneficial longer term treatment outcome in children with ADHD (Block et al. 2010).

No studies have so far investigated predictors of response to atomoxetine in children and adolescents with ASD and concomitant ADHD symptoms. This was therefore the aim of the present analysis, based on data of our double-blind placebo-controlled 8-week trial, which was followed by an open label 20-week extension period.

Study design & participants

The study contained two phases. The first phase was an 8-week randomized double blind trial of atomoxetine versus placebo. Patients who had completed the placebo-controlled trial entered the second phase, an open-label extension, without disclosing the treatment allocation of the preceding eight week trial. 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 20 weeks of treatment with atomoxetine. For both groups we had assessments at baseline and after 5 and 8 weeks of treatment.

Participants had to be between 6 and 17 years, to have an intelligence quotient of at least 60, and to have a dual diagnosis of ASD and ADHD. ASD diagnosis was based on clinical assessment and corroborated by at least two subscale scores on the Autism Diagnostic Interview Revised (ADI-R; Rutter et all. 2003) above the cut-off; ADHD diagnoses had to meet DSM-IV-TR criteria A through D for ADHD any type. Exclusion criteria included a weight of less than 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 in-patient treatment.

Parents and children of 12 years and older all provided written informed consent, while younger children had given their assent. The study had been approved by the national and local institutional review board committees.

The primary outcome measure was the investigator-administered total ADHD-RS score, a DSM-IV based rating scale containing 18 items on inattentive and hyperactive-impulsive symptoms to be scored on a four-point scale over the past week. The total score is the sum of the scores on each of the 18 items (Du Paul et all. 1998).

Demographic information of participants with complete data after 8 weeks of atomoxetine treatment is displayed in table 1.

Predictor	Demographics	p-value	η^2
Male sex, n (%)	75 (87.2)	.19	.02
Age, mean (SD) in years	9.96 (2.83)	.77	.10
IQ, mean (SD)	92.6 (17.1)	.16	.66
Previous psychopharmacological treatment, n (%)	53 (61.6)	.28	.01
CYP2D6 genotype, n (%)[1]		.98	.001
Poor	10 (11.6)		
Intermediate	24 (27.9)		
Extensive	51 (59.3)		
Ultra-rapid	0 (0)		
Type of ASD, n (%)		.17	.02
PDD-NOS/ Asperger's disorder	35 (40.7)		
Autistic disorder	51 (59,3)		

Table 1. Results of repeated measures ANOVA with the ADHD-RS total score at baseline and week 8 as the repeated outcome measure in participants with complete data after 8 weeks of treatment with atomoxetine

[1]One missing genotype

Abbreviations: SD=standard deviation, IQ=intelligence quotient, ASD=autism spectrum disorder, PDD-NOS=Pervasive Developmental Disorder-Not Otherwise Specified

Data analysis

We combined all patients into one group; for the group originally allocated to atomoxetine and who had completed the first 8 weeks of the study (*n*=43) we considered the first 8 weeks of the study and for the group originally allocated to placebo and who had completed the first 8 weeks of the open label extension period (*n*=43) the first 8 weeks of the open label extension period. The data were analyzed with repeated measures ANOVA, with the ADHD-RS total score at baseline and week 8 as the repeated outcome measure. The baseline characteristics considered as predictor variables were sex, age, IQ (based on the Wechsler Intelligence Scale), presence or absence of previous psychopharmacological treatment (both psychostimulants and antipsychotics), *CYP2D6* genotype (poor, intermediate, extensive, or ultra-rapid metabolizer), and type of ASD (Autistic Disorder versus other DSM-IV-TR pervasive developmental disorders [Asperger's Disorder and Pervasive Developmental Disorder Not Otherwise Specified]). A p-value of 0.05 for the time x predictor term was considered evidence for a moderating effect of the predictor on treatment.

We additionally investigated whether an early response to treatment predicts the further treatment course. In line with Newcorn et al. (2009), we defined early response as a 25% or greater reduction of the ADHD-RS total score from baseline after 5 weeks of atomoxetine treatment. Subsequently, we entered ADHD-RS scores at week 5 and week 8 as the repeated outcome measure and analyzed whether early response (yes n= 51; no n=35) was a significant predictor of the treatment course.

Results

None of the baseline characteristics were found to be a predictor of clinical response to atomoxetine in this study, see table 1.

However, early response was a significant moderator of treatment course (p=.004). Within-group analyses revealed that participants with an early response after 5 weeks remained stable in the following 3 weeks (p=0.21), whereas participants without an early response showed a significant decrease in ADHD-RS total score from week 5 to 8 (p=0.003).

Discussion

The present study did not identify any demographic or clinical factors associated with a more favorable response to atomoxetine in children and adolescents with ASD and ADHD symptoms. By and large this is in line with findings in typical ADHD (without ASD), where also none of these factors were associated with treatment response (Newcorn et all. 2009). However, a meta-analysis across nine randomized placebo-controlled trials in children with ADHD did indicate that atomoxetine is more effective in female patients (Cheng et all. 2007), which we did not observe.

Previous studies had also suggested that treatment naïve children and adolescents with ADHD have better response to atomoxetine treatment (Montoya et al. 2009; Svanborg et al. 2009; Bushe and Savill 2014). Although we had a sizeable proportion of participants who were treatment naïve (n=36, i.e. 36%), we did not find any significant effect of previous treatment status. Of note, a recent study had also indicated that the effect of atomoxetine was largely independent of previous exposure to psychostimulants when looking at a continuous performance test combined with an infrared motion tracking device as outcome measure (Wehmeier et al. 2014).

We also found no differences in response to atomoxetine between children with Autistic Disorder (n=51) versus those with less severe DSM-IV-TR ASD variants (Asperger's

Disorder or PDDNOS; n=35). This similar efficacy of atomoxetine in children with Autistic Disorder is in contrast with a small scale open label study showing no benefits of atomoxetine treatment in twelve children with a severe form of autistic disorder and ADHD symptoms (Charnsil 2011).

Interestingly, we still observed further improvement in ADHD symptoms even when there was minimal or less response after the first five weeks of treatment. This result is in line with our previous findings that patients with ASD tend to require more time for a full response to atomoxetine, with further gains in symptom improvement associated with continued treatment with atomoxetine also beyond 8 weeks (Harfterkamp et al. 2013). Thus, whereas studies in patients with ADHD had indicated an association between early response and overall longer term response at trial completion (Newcorn et al. 2009; Block et al. 2010), our study suggests that in children with ASD an early response is less indicative of final response. This has clear clinical implications in that clinicians should allow sufficient time when treating ADHD symptoms in children with ASD with atomoxetine, before concluding lack of response.

The most important limitation of the present study is its modest sample size, even if it was based on the largest controlled study of atomoxetine in patients with ASD to date. It cannot be excluded that a larger sample size would have allowed identification of some predictors of treatment response. However, as our results were far from approaching statistical significance it is not likely that we have missed predictors with a clinically meaningful effect size.

In summary, we did not identify any demographic or clinical factors associated with a more favorable response to atomoxetine in children and adolescents with ASD and ADHD symptoms. However, in contrast to previous findings in children and adolescents with only ADHD our findings showed that lack of early response does not mean lack of response. Participants without an early response still showed a significant decrease in the ADHD-RS in the subsequent weeks of treatment.

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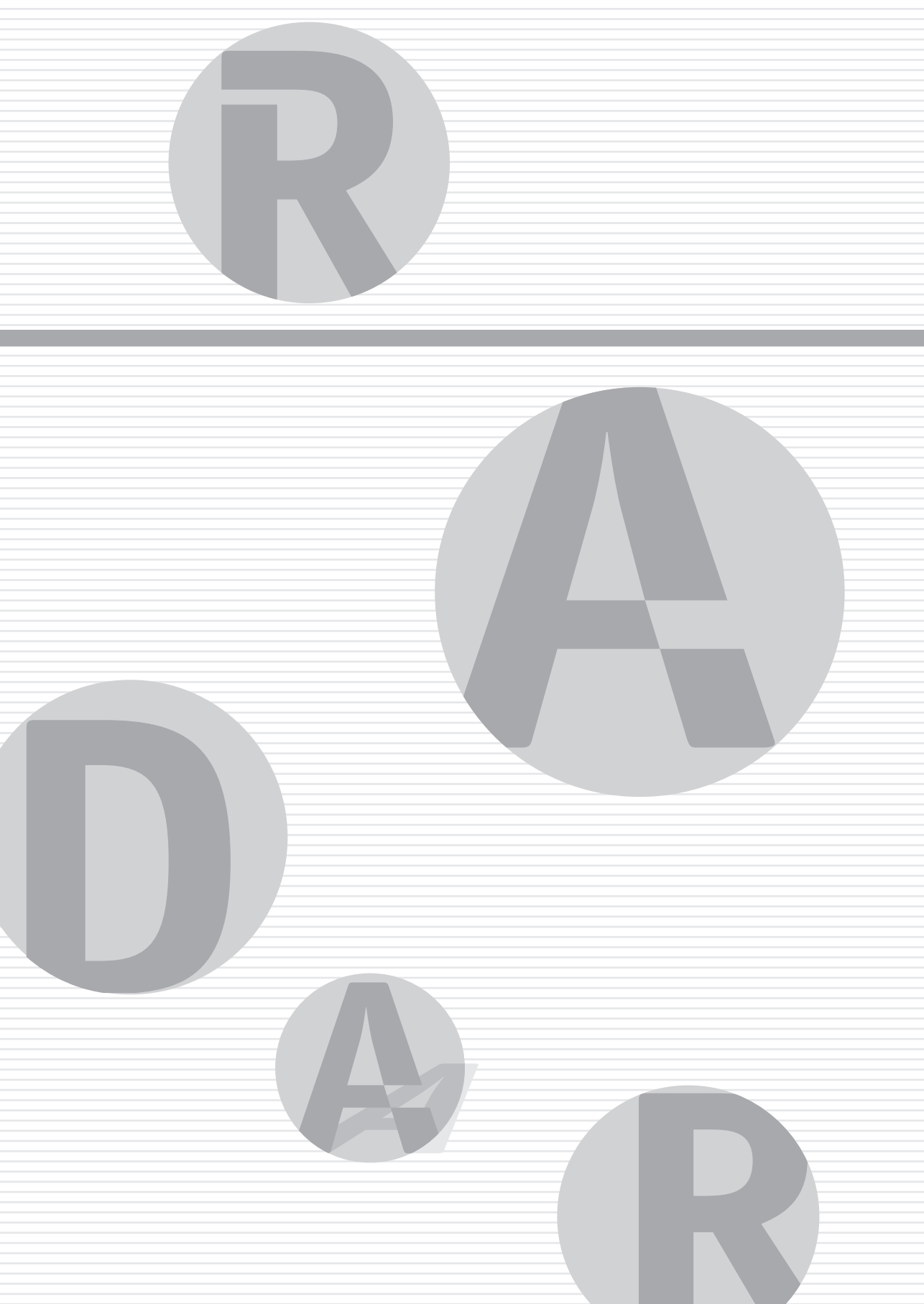
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Chapter 7

Summary and General Discussion

This final chapter provides an overall summary and discussion of the findings of our study entitled **R**esearch on **A**tomoxetine in **D**utch **A**SD/ADHD Child**r**en (RADAR), including an indication of the clinical relevance and suggestions for future research.

Introduction

Autism Spectrum Disorder (ASD) is a complex developmental disorder, characterized, in varying degrees, by difficulties in social interaction, verbal and nonverbal communication, and repetitive behaviors. In the fifth version of the Diagnostic and Statistical manual of Mental Disorders (DSM-5), published in May 2013 all pervasive developmental disorders were merged into one umbrella diagnosis of ASD. Previously, distinct disorders were distinguished, including autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder-not otherwise specified (PDD-NOS). ASD is often associated with intellectual disability, difficulties in motor coordination, physical health issues such as sleep and gastrointestinal disturbances, and attention and behavior problems. The most common coexisting diagnoses comprise emotional disorders, and in about one third of patients attention deficit/hyperactivity disorder (ADHD) can be diagnosed (Rommelse, Geurts et al. 2011; Rybakowski, Bialek et al. 2014).

In this thesis I have presented the findings of the RADAR study which has investigated the effects of atomoxetine in children and adolescents with ASD on ADHD symptoms. The chosen design was an 8 weeks double blind placebo controlled trial, followed by 20 weeks open label extension treatment. During the placebo controlled period we also assessed the effect of atomoxetine on cognitive functioning (especially inhibitory control) and on social functioning, and we tried to identify predictors of positive treatment effects with atomoxetine.

Since the start of our RADAR study in 2005 several other investigators also studied the effect of atomoxetine on ADHD symptoms in children and adolescents with ASD. In 2006 an 8 week open label study evaluated the effect of atomoxetine in 16 children and adolescents with ASD. No concomitant psychotropic drug was allowed during these 8 weeks. The primary measure was the Clinical Global Impression-Improvement Scale (CGI-I) rated at baseline and after 8 weeks. Twelve participants were considered responders to treatment with a rating of very much improved or much improved (Posey, Wiegand et al. 2006). Since 2010 three additional studies with the same goal have been conducted (Charnsil, 2010; Zeiner, Gjevik et al 2011; Fernández-Jaén, Fernández-Mayoralas et al 2013). Charnsil (2010) examined the effect of 10 weeks open label treatment with atomoxetine in 12 children with a severe autistic disorder and ADHD symptoms. Both the Aberrant Behavior Checklist; Hyperactivity scale (ABC-H) and the

CGI-I showed no improvement on ADHD symptoms. Autistic diagnoses were established using the Childhood Autism Rating Scale (CARS) and the diagnoses were confirmed by a child psychiatrist using Diagnostic and Statistical Manual of Mental Disorders fourth edition, text revised (DSM-IV-TR) criteria. The results suggested that children with a severe autistic disorder and co-occurring ADHD may not benefit from atomoxetine. Zeiner (2011) enrolled 14 boys between 7 and 17 years with ASD and ADHD symptoms in a 10 week open label study with atomoxetine. Measurements were the ADHD-rating scale (ADHD-RS) and the CGI-I. Seven participants were classified as clinical responder with regard to ADHD symptoms. Finally, Fernández-Jaén (2013) studied the efficacy and tolerability of atomoxetine in 24 children and adolescents with ASD and ADHD symptoms in a 16 week open label study. Measurements were done with the CGI-I and the Conners Teacher Rating Scale-Revised: Short Form (CTRS-R:S). Of the 23 participants who completed the study 17 children showed improvement and only 5 participants presented adverse events. These small open-label studies confirmed the suggestion that atomoxetine might be a promising medicine to treat ADHD symptoms in children and adolescents with ASD.

Results of the RADAR study

The study Sample

In 2005 we started our study to investigate the effect of atomoxetine on ADHD symptoms in children and adolescents with ASD compared to placebo in an 8 week double blind trial followed by a 20 week open label extension period. Up to now, this has been the largest and sole adequately powered placebo-controlled study examining the efficacy and safety of atomoxetine for symptoms of ADHD in children with ASD.

In chapter 2 and 3 we have described the baseline characteristics of our study sample. In summary we included mainly Caucasian male participants (85%) with a mean age of 10 years and a Wechsler intelligence quotient of 94. One third of them had never used psychopharmacological treatment before. Two participants did not meet ADI-R criteria for ASD, but were enrolled purely based on clinician's judgment; 60% were classified as having an autistic disorder, 5% as having Asperger's disorder, and 33% as PDDNOS (Chapter 2).

Of the 97 children 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 children remained on atomoxetine during the entire planned extension phase; 15 discontinued for a variety of reasons (Chapter 3).

A Randomized Double-blind Study of Atomoxetine Versus Placebo for ADHD Symptoms in Children with ASD (Chapter 2)

Our aim was to test the hypothesis that atomoxetine would be superior to placebo on the clinician-based ADHD rating scale (ADHD-RS) and well tolerated in children and adolescents with ASD.

Our findings showed that atomoxetine was superior to placebo after a treatment period of 8 weeks; the ADHD-RS total and subscale scores had improved significantly more in the atomoxetine than in the placebo group, with a larger benefit on the hyperactivity-impulsivity domain. Teacher ratings on the CTRS-R:S also indicated a larger improvement on hyperactive symptoms, with only trend-level improvements in cognitive/inattention symptoms. This is in line with the findings in a 6 weeks placebo controlled trial that also found clinician-rated improvement in hyperactivity symptoms, but only trend-level improvement in inattentive symptoms in children with ASD (Arnold, Aman et al. 2006). However, this was in contrast with the effects of atomoxetine in children with typical ADHD, where similar effect sizes on hyperactivity and inattention have been reported (Schwartz and Corell 2014; Svanborg, Thernlund et al. 2009; Biederman, Gao et al. 2006).

The magnitude of the effect of atomoxetine appeared to be smaller in children with ASD than in children with typical ADHD. In our study, the mean change from baseline in the ADHD-RS total score was 8.2 points, i.e., an effect size of 0,9, whereas the change from baseline in the ADHD-RS total score in children with typical ADHD has repeatedly been found to be in the range of 13-19 points, ,i.e., an almost twice as large effect size (Schwartz and Corell 2014; Svanborg, Thernlund et al. 2009; Biederman, Gao et al. 2006).

Also, only a small proportion (around 20%) of children improved much or very much on atomoxetine as rated by the CGI-ADHD-I. Actually, in our study, the proportion of patients on atomoxetine who clearly improved did not differ significantly from the placebo group. The overall modest CGI results may be due to the CGI reflecting an overall change of ADHD status in the context of a complex comorbid condition of ASD and ADHD, whereas the ADHD symptoms score changes are more specific. This highlights the difficulty of treating ADHD symptoms in children with ASD.

Atomoxetine was generally well tolerated in our group of children and adolescents with ASD and ADHD. We encountered no serious adverse events. Only one patient in the atomoxetine group discontinued because of a (nonserious) adverse event. Reported adverse events, such as fatigue, decreased appetite, nausea, abdominal pain and vomiting in this study population were in line with those previously reported (Cheng, Chen et al. 2007; Schwartz and Corell 2014; Eli Lilly product characteristics). Within our group of patients, however, the frequency of adverse events tended to be somewhat higher than

described in the atomoxetine summary of product characteristics, especially regarding occurrence of fatigue, nausea, decreased appetite, and early morning awakenings.

Effect of atomoxetine on ADHD symptoms in a 20 weeks open label treatment after fulfilling the 8 weeks double blind placebo controlled period (Chapter 3)

Our goal was to test the hypothesis that continued treatment with atomoxetine for ADHD symptoms in children and adolescents with ASD beyond eight weeks would led to a further decrease of clinician-rated ADHD symptoms, whilst we expected adverse events to subside over time.

The open label follow up with 88 participants with ASD receiving treatment with atomoxetine for 20 additional weeks indeed resulted in further improvements in hyperactivity/impulsivity and inattention symptoms in children. Of these 88 participants 46 had received a total of 20 weeks treatment with atomoxetine (the originally placebo group) and 42 participants had received treatment with atomoxetine during the entire study course of 28 weeks (the original atomoxetine group). These data suggest that continued treatment beyond 8 weeks with atomoxetine ads to further improvement of ADHD symptoms in children with comorbid ASD. This is in contrast with the situation in children with typical ADHD, where no further improvement after 3 months of treatment has been seen according to a pooled data analysis of 13 clinical trials (Wilens, Newcorn et al. 2006). Our findings thus indicate that in patients with ASD and ADHD it takes clearly more time than in children with typical ADHD before their full response to atomoxetine is established. This is probably due to a different pathophysiological background of ADHD symptoms in children with ASD.

In Chapter 2 we described a more pronounced effect on hyperactivity-impulsivity than on inattention symptoms. After 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 (Adler, Spencer et al. 2009; Wilens, Newcorn et al. 2006). We need more studies to explain these differential effects, e.g., by means of neuroimaging studies.

Adverse events diminished during increased open label treatment with atomoxetine, especially nausea and fatigue, which both were clearly less frequently reported than during the first 8 weeks of treatment. This finding is similar in treatment studies with atomoxetine in patients with typical ADHD, which also showed a reduction in adverse events over time (Kratochvil, Wilens et al. 2006; Donnely, Bangs et al. 2009; Wilens, Newcorn et al. 2006). More than 75% of all patients starting our trial completed the whole study. Discontinuation due to 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 six month double blind trial of treatment with atomoxetine in adults with ADHD (n=491), where a discontinuation of 17.2% due to adverse events in the atomoxetine group was observed (Adler, Spencer et al. 2009).

A Randomized, Double-blind Comparison of Atomoxetine and Placebo on Response Inhibition and Interference Control in Children and Adolescents with Autism Spectrum Disorder and comorbid Attention-Deficit/Hyperactivity Disorder symptoms (Chapter 4)

The aims of the study described in chapter 4 were to examine whether atomoxetine improved two forms of inhibitory control (response inhibition and interference control), and whether ADHD symptom improvement was mediated by improvements in inhibitory control. Response inhibition is best described as an output-process reflecting stimulus selection, whereas interference control is input-dependent, reflecting response organization. Our study demonstrated selective beneficial effects of atomoxetine on response inhibition but not interference control in children and adolescents with both ASD and ADHD. The first finding is in line with a previous study documenting response inhibition in children with ADHD (Gau and Shang, 2010) and with the finding that atomoxetine treatment in adult patients was associated with shorter stop-signal reaction times and lower numbers of commission errors on a sustained attention task (Chamberlain, Del Campo et al., 2007). However, in our study an effect of atomoxetine on interference control was absent, which is in disagreement with some previous studies examining the effect of atomoxetine on interference control in ADHD patients (Yang, Cao et al. 2011) but is in line with others (Schwartz and Verhaeghen 2008). The neural substrates of response inhibition (an output-process reflecting stimulus selection), and interference control (an input-dependent process reflecting response organization) in ADHD are not yet fully understood. An explanation could be that atomoxetine mainly exerts its effects on the prefrontal cortex underlying response inhibition and not on the parietal brain regions also required for interference control in patients with ASD and ADHD symptoms (Vaidya, Bunge et al. 2005; Durston, Mulder et al. 2006; Bunge, Hazeltine et al. 2002).

Our study also showed that participants improving in response inhibition were not necessarily those, who also showed improvement on ADHD symptoms. This may suggest that monitoring treatment response of atomoxetine on ADHD symptoms in children with ASD using inhibitory control tasks or other cognitive tests may have some added clinical utility. In addition, it is also possible that improvement of cognitive processes will have a more positive impact on the day-to-day functioning of these children than improvement of ADHD symptoms.

Atomoxetine in Autism Spectrum Disorder: no effects on social functioning, some benefits on stereotyped behaviors, inappropriate speech, and fear of change (Chapter 5)

The study described in chapter 5 investigated possible effects of atomoxetine on ASD symptoms in children with ASD and ADHD symptoms. We used parent-based secondary outcome rating scales, i.e., the Aberrant Behavior Checklist (ABC) (Aman, Singh et al. 1985) and the Children's Social Behavior Questionnaire (CSBQ) (Hartman, Luteijn et al. 2006) as part of our 8 week double-blind placebo-controlled trial.

Our study showed no treatment effects on the core ASD symptom domains as indicated by lack of improvements on the CSBQ subscales Not Tuned, Reduced Contact, and Social Information. Still, we did find some indication of benefits following treatment with atomoxetine on the ABC subscales stereotyped behaviors, inappropriate speech, hyperactivity and on the CSBQ subscale fear of change. Obviously, the effect on the ABC Hyperactivity subscale is directly related to improvements on ADHD symptoms in line with our findings described in chapter 2 and 3. The effect of atomoxetine on stereotyped behaviors, inappropriate speech, and fear of change suggests that atomoxetine may improve restricted and stereotyped behaviors and communication. It must be noted that the affected subscales contains only 7, 4, and 3 items, respectively, therefore a statistically significant improvement in this case is not likely to be clinically meaningful.

No evidence for predictors of response to atomoxetine treatment of Attention-Deficit/Hyperactivity Disorder symptoms in children and adolescents with Autism Spectrum Disorder (Chapter 6)

The aim of the analysis described in chapter 6 was to investigate predictors of response to atomoxetine in children and adolescents with ASD and concomitant ADHD symptoms. We combined all patients into one group; for the group originally allocated to atomoxetine and who had completed the first 8 weeks of the study (n=43) we considered the first 8 weeks of the study and for the group originally allocated to placebo and who had completed the first 8 weeks of the open label extension period (n=43) the first 8 weeks of the open label extension period. We did not identify any demographic or clinical factors associated with a more favorable response to atomoxetine in children and adolescents with ASD and ADHD symptoms. By and large this is in line with findings in typical ADHD (without ASD), where also none of these factors was associated with treatment response (Newcorn, Sutton et al. 2009). Studies in patients with ADHD had indicated an association between early response and overall longer term response at trial completion (Newcorn, Sutton et al. 2009; Block, Williams et al. 2010). We observed further improvement in ADHD symptoms even when there was minimal or less response after the first five weeks of treatment. This result is in line with our previous findings

that patients with ASD tend to require more time for a full response to atomoxetine, with further gains in symptom improvement associated with continued treatment with atomoxetine also beyond 8 weeks, as described in chapter 3.

Brief listing of clinical relevance

The presence of symptoms of attention deficit/hyperactivity disorder (ADHD) in children with an autism spectrum disorder (ASD) is a serious clinical problem and frequently complicates these children's therapeutic management. Appropriate medication in patients with ASD with ADHD symptoms might enhance the child's ability to benefit from educational and behavior modification interventions.

Our study showed that atomoxetine is effective on ADHD symptoms in children with ASD, with ongoing improvement during continued treatment until 28 weeks. In the first 8 weeks we observed a relative stronger effect on hyperactivity-impulsivity symptom domain, however in the following 20 weeks we found similar effects on both the hyperactivity-impulsivity and the inattentive symptoms domains.

We also found further improvement in ADHD symptoms even when there was minimal or less response after the first five weeks of treatment. Our study suggests that in children with ASD an early response is less indicative of final response.

We showed that atomoxetine is well tolerated in children with ASD and that adverse events diminish after time. We found no indication to support the use of genotyping to guide clinical use.

Therefore, clinicians should be patient when treating ADHD symptoms in children with ASD with atomoxetine, before concluding lack of response. Future studies may want to investigate if higher than usual doses might be of benefit in some cases.

Currently atomoxetine is recommended as second line treatment for children with ADHD, who have responded unfavorably to psychostimulants. The current study implies that this would also be a valid recommendation for children with ASD and ADHD.

List of limitations

The findings in our study should be seen in the context of several limitations:

A first limitation is the assessment of ADHD and ASD. For the diagnosis of ADHD, we relied on routine clinical procedures and did not use a formal diagnostic interview. Also, we did not analyze teacher-based ratings to establish a diagnosis of ADHD, but relied solely on clinician-based overall ratings of ADHD symptoms. Therefore we ignored a relevant

DSM-IV-TR and DSM 5 criterion. Moreover, ASD diagnoses had to be corroborated by algorithm cut-off scores on the ADI-R, but we allowed inclusion of children who did not meet ADI-R cut-off scores on the social interaction domain, in deviation from DSM-IV-TR criteria for Pervasive Developmental Disorder Not Otherwise Specified.

A second limitation was the duration of the double blind placebo-controlled period of 8 weeks, which may have been be too short for atomoxetine to reach its full effect. Our open label extension study suggested that the full effect of atomoxetine on ADHD symptoms in children and adolescents with ASD may require up to 28 weeks of atomoxetine administration. A longer placebo-controlled period could also clarify whether rates of adverse events would wane over time.

A third limitation is the reliability of the teacher ratings may have been limited by some measurement error due to missing teacher reports and transition of children to new classes with different teachers.

A fourth limitation are the disadvantages associated with open label studies. In the 20 week duration open label period the lack of a control group made it hard to distinguish between natural course and regression towards the mean versus true treatment effects.

A fifth limitation may have been the fact that we did not use standardized rating scales to assess adverse events, but used open-ended questioning. We may thus have missed adverse events, such as dysthymia. However, this method of assessing adverse events is in line with other trials involving atomoxetine and makes the findings comparable.

A sixth limitation may have been the choice of rating scales to assess improvements on ASD symptoms. For this, we relied entirely on parent-ratings, without clinical assessment, observation, or use of teacher ratings. However, the ABC has become something of a gold standard for trials in this area. Future studies may use more refined ratings scales such as the social responsiveness scale (Constantino and Todd, 2003)

A seventh limitation has been that the study had not been primarily powered to investigate improvements on social behavior nor as a study aimed at investigating predictors of response to atomoxetine in children and adolescents with ASD and concomitant ADHD symptoms. It therefore cannot be excluded that a larger sample size would have indicated effects of atomoxetine on social behavior, and would have allowed the identification of some predictors of treatment response of atomoxetine.

An eighth and final limitation has been our study sample, which had relatively few adolescents, few female subjects, and few children with IQs in the lower range, making findings possibly less generalizable for these groups.

Recommendations for future research

Atomoxetine appears to be a promising treatment of ADHD in children and adolescents with ASD, but only two RCT's has been conducted. The first RCT was limited by a small sample size (n=16, Arnold, Aman et al. 2006). Our RCT recruited a much larger sample (n=97) and incorporated a long-term follow-up, but relied solely on parent and clinician ratings as measures of outcome (Chapter 2 and 3 of this thesis). Clearly more RCT's with atomoxetine in children with ASD are needed. As outcome measures, ratings of participants, parents, teachers, and investigators should all be taken in consideration.

We found several differences in outcome between children with ADHD symptoms and ASD compared to children with only ADHD. The response rate of atomoxetine appeared to be smaller in children with ASD than in children with typical ADHD. The frequency of adverse events in the first weeks of treatment was higher than in children with ADHD. Both findings are in line with results of a trial using methylphenidate to treat ADHD symptoms in children with ASD (RUPP 2005). We found a larger improvement on hyperactive symptoms, with only trend-level improvements in cognitive/inattention symptoms in the first 8 weeks of our study, whereas in children with typical ADHD similar effect sizes on hyperactivity and inattention have been reported after treatment with atomoxetine (Schwartz and Corell 2014; Svanborg, Thernlund et al. 2009; Biederman, Gao et al. 2006). Also our findings indicate that patients with ASD and ADHD need clearly more time than children with typical ADHD before their full response to atomoxetine is established (Chapter 3, this thesis). We observed further improvement in ADHD symptoms even when there was minimal or less response after the first five weeks of treatment in contrast to patients with only ADHD where an association between early response and overall longer term response was found (Newcorn, Sutton et al. 2009; Block, Williams et al. 2010). ADHD may be seen as a milder subtype within the ASD spectrum (van der Meer; Oerlemans et al. 2012) and that children with ASD are more impaired and vulnerable. Another possibility is a different pathophysiological background of ADHD symptoms in children with ASD. More research is needed to understand the differing response to medication between children with only ADHD and those with ADHD and ASD.

Direct comparisons between psychostimulants and atomoxetine regarding effects in children with ASD would be recommendable. Comparison of effects is in this thesis hampered by the fact that the RUPP methylphenidate study used different outcome measures. Currently we lack guidance on which compound should be used first. Given the rapid onset of action of methylphenidate, starting with methylphenidate may be a good strategy.

Future studies could investigate if adjustments to dosage atomoxetine, such as splitting the daily dose initially, starting lower than recommended or even higher than usual and escalating slowly may be of benefit in some cases.

Our expectation that children and adolescents with ASD who have responded favorably to treatment with atomoxetine might profit more from behavioral interventions needs to be formally investigated in future studies, preferably in a RCT.

In this thesis some benefits on stereotyped behaviors, inappropriate speech, and fear of change have been described. Also, some other small scaled studies suggested improvements in core ASD symptoms and social functioning (Arnold, Aman et al. 2006 and Posey, Wiegand et al. 2006). Therefore, it would be worthwhile to design a study specifically to investigate the effect of atomoxetine on social behavior.

Finally, it would also be important to do more publicly funded and designed studies, without involvement of the pharmaceutical industry as pharmaceutical companies may design studies in such a way that chances of unfavorable outcomes are minimized.

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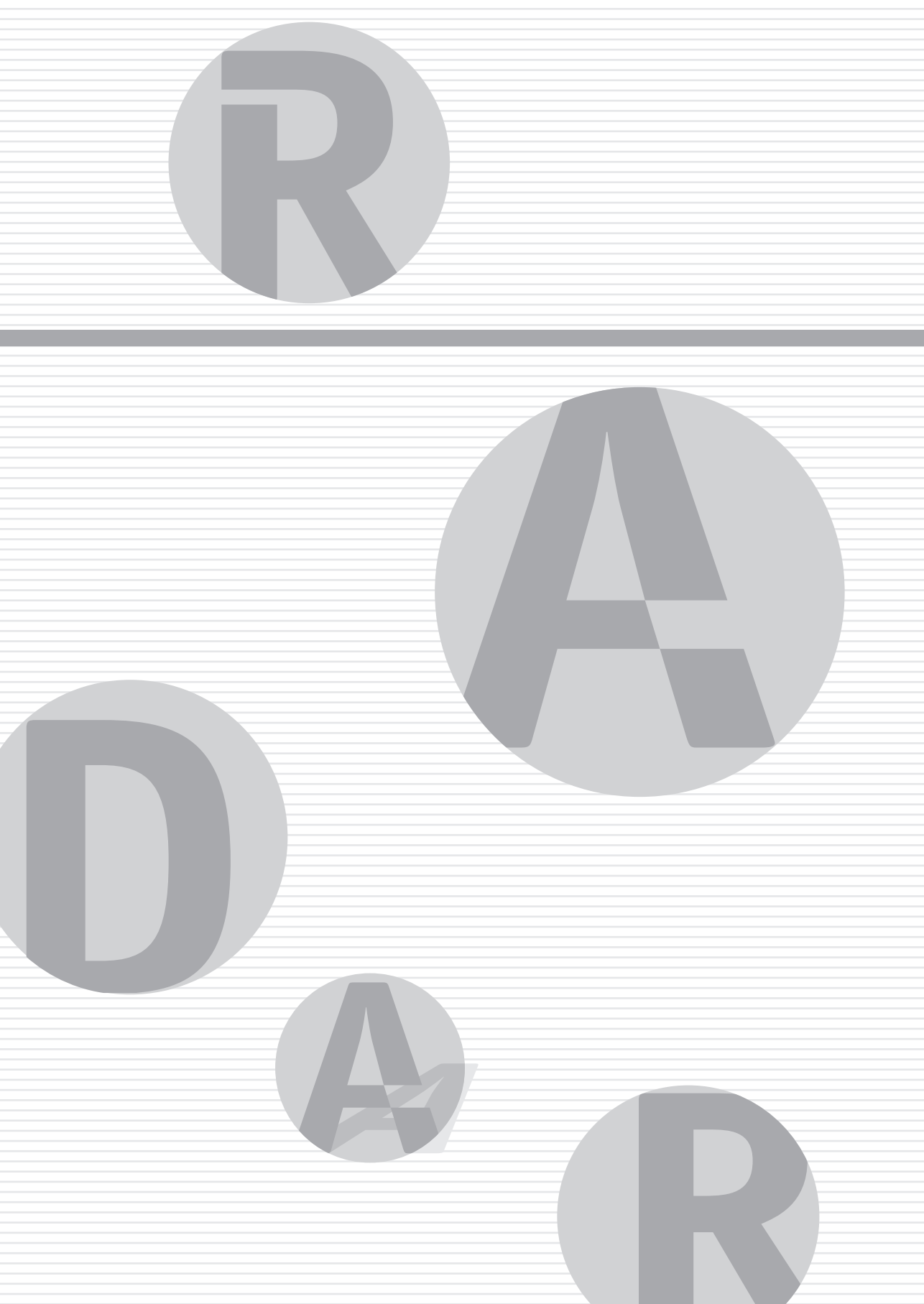
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Chapter 8

Summary in Dutch / Nederlandse samenvatting

Inleiding

Een autisme spectrum stoornis (ASS) is een ontwikkelingsstoornis, gekenmerkt door problemen in de sociale interactie, verbale en non-verbale communicatie, samengaand met repetitief/stereotiep gedrag. Er worden verschillende vormen van ASS onderscheiden, zoals de autistische stoornis, het syndroom van Asperger en de pervasieve ontwikkelingsstoornis niet anderszins omschreven (PDD-NOS). In de vijfde versie van het handboek voor psychiatrie; de Diagnostic and Statistical manual of Mental Disorders (DSM-5) gepubliceerd in mei 2013, zijn alle autisme spectrum stoornissen samengevoegd tot één paraplu diagnose van ASS.

Een ASS komt vaak samen voor met een verstandelijke beperking, moeilijkheden in motorische coördinatie, lichamelijke gezondheidsproblemen zoals slaapstoornissen, maagdarmproblemen, concentratiestoornissen en gedragsproblemen. Bij ongeveer een derde van de patiënten met een ASS kan ook de diagnose aandachtstekortstoornis met hyperactiviteit (ADHD) worden gesteld. Mensen met ADHD hebben vaker en sterker dan de meeste anderen problemen met het richten van hun aandacht en zijn snel afgeleid (concentratieproblemen), ze zijn voortdurend in beweging, ervaren veelal een grote onrust (hyperactiviteit) en zij doen eerst en denken daarna (impulsiviteit).

De aanwezigheid van ADHD symptomen bij mensen met een ASS leidt tot meer beperkingen in het dagelijks leven. Deze mensen hebben vaker gedragsproblemen, meer moeite met concentreren, kunnen informatie minder goed verwerken, laten vaker auto mutilerend gedrag zien en hebben vaker last van veranderingen dan mensen met alleen een ASS. Ook zijn zij minder leerbaar en minder gevoelig voor gedragstherapeutische interventies. Behandeling van de ADHD symptomen met de juiste medicatie bij mensen met zowel een ASS als ADHD kan leiden tot vermindering van de ADHD symptomen, waardoor ze wellicht meer kunnen profiteren van educatieve en gedragstherapeutische behandeling.

Er zijn weinig studies gepubliceerd die onderzoek hebben gedaan naar de medicamenteuze behandeling van ADHD symptomen bij mensen met een ASS. Veelal worden mensen met een ASS uitgesloten van deelname aan dergelijke studies. In dit proefschrift worden het onderzoek en de uitkomsten naar de effecten van atomoxetine, een niet stimulerend medicament voor de behandeling van ADHD symptomen, bij kinderen[1] tussen de 6 en de 18 jaar beschreven. We noemen onze studie de RADAR studie (**R**esearch on **A**tomoxetine in **D**utch **A**SD/ADHD Chil**r**en).

In de voorlaatste versie van de DSM, de DSM-IV-TR, die in 2005 gangbaar was, mocht de diagnose ADHD niet gesteld worden als er sprake was één van de vormen

[1] Lees kinderen en adolescenten (6-18 jaar) daar waar kinderen staat.

van autisme, vandaar dat in dit proefschrift gesproken wordt over de aanwezigheid van ADHD symptomen bij kinderen met een ASS.

Medicamenteuze behandeling van ADHD symptomen bij kinderen met een ASS

Er zijn verschillende groepen van medicijnen die regelmatig worden voorgeschreven aan kinderen met een ASS. Ik geef een kort overzicht van de belangrijkste bevindingen.

Psychostimulantia, zoals methylfenidaat (Ritalin®) en dexamfetamine zijn de meest bekende medicamenten in de behandeling van ADHD. Er is slechts weinig onderzoek naar het effect van deze middelen bij kinderen met een ASS. Het grootste onderzoek is in 2005 uitgevoerd door de Research Units on Pediatric Psychopharmacology Autism Network (RUPP), die een dubbel blind placebo gecontroleerde[2] studie hebben uitgevoerd bij 72 kinderen met ASS en ADHD. Uit dit onderzoek kwam naar voren dat het effect van behandeling op ADHD symptomen met methylfenidaat kleiner is dan bij kinderen met alleen ADHD en dat deze kinderen gevoeliger zijn voor bijwerkingen.

Antipsychotica, zoals risperidon (Risperdal®) en aripiprazol (Abilify®) worden vaak gegeven aan kinderen met een ASS voor de behandeling van opstandig gedrag, agressie en/of hyperactiviteit en impulsiviteit. Studies met deze middelen bij kinderen met een ASS hebben laten zien dat er effect is op gedragsproblemen en hyperactiviteit, maar geen effect op de concentratieproblemen. Tevens blijken deze middelen op korte en lange termijn vervelende bijwerkingen te hebben, zoals gewichtstoename, kans op ontstaan van het metabool syndroom en extrapiramidale bijwerkingen, zoals een tremor en acathisie.

Atomoxetine (Strattera®) is een noradrenerge heropname remmer die in 2005 in Nederland is geregistreerd voor de behandeling van ADHD bij kinderen tussen de 6 en 18 jaar. Sinds 2005 zijn er zeven studies uitgevoerd waarbij gekeken werd naar de effecten van behandeling met atomoxetine bij kinderen met zowel ASS als ADHD. Het waren allemaal studies met een gering aantal deelnemers. Er was slechts één dubbel blind placebo gecontroleerde studie gedaan, bij 16 kinderen, waarbij gebruik van andere medicatie echter wel werd toegestaan. Voorafgaande aan onze studie is in het UCKJP Accare Groningen een open label[3] studie met atomoxetine van 10 weken uitgevoerd door Pieter Troost, kinder- en jeugdpsychiater. Deze studie was feitelijk de pilot studie voor onze studie. Er namen 12 kinderen deel aan deze studie, die geen andere medicatie

[2] Dubbel blind placebo gecontroleerd wil zeggen dat zowel onderzoekers als deelnemers niet weten of het echte medicijn of een placebo ("nepmedicijn") ingenomen wordt.

[3] Open Label betekent dat iedereen weet welk medicijn gegeven wordt.

mochten gebruiken. Zeven kinderen hebben de studie afgerond en zij waren allemaal "veel" of zelfs "heel veel" verbeterd wat betreft hun ADHD symptomen.

De vijf kinderen die gestopt zijn, zijn allemaal gestopt vanwege bijwerkingen, zoals moeheid, maagdarmproblemen en snel geïrriteerd zijn, maar niet vanwege een gebrek aan werkzaamheid.

Opzet RADAR studie

De RADAR studie bestond uit drie delen. Voorafgaande aan de daadwerkelijke start van de studie werden de reeds gestelde diagnoses ASS en ADHD bevestigd door de afname van gestructureerde interviews. Kinderen die gedragsbeïnvloedende medicatie gebruikten, moesten in deze periode het gebruik daarvan afbouwen en ermee stoppen. Vervolgens volgde een dubbel blind placebo gecontroleerde fase van 8 weken, waarin kinderen gedurende 8 weken behandeld werden met atomoxetine of een placebo. Alle kinderen die deze fase hadden afgerond werden uitgenodigd voor de derde fase, die bestond uit 20 weken open label behandeling met atomoxetine. Kinderen en onderzoekers hebben nooit geweten of zij in de eerste 8 weken atomoxetine of een placebo hadden of hebben voorgeschreven.

De studie is uitgevoerd in negen centra in Nederland. In totaal zijn 97 kinderen gestart aan de studie en hebben 73 kinderen de hele studie doorlopen.

Bevindingen

In *Hoofdstuk 2* beschrijven we het beloop en de resultaten van de 8 weken durende dubbel blind placebo gecontroleerde fase. In deze fase hebben we het effect van atomoxetine op ADHD symptomen onderzocht en hebben we onderzocht of atomoxetine goed verdragen werd door kinderen met een ASS. Dat hebben we onderzocht door de kinderen regelmatig terug te laten komen bij de onderzoekers en hen te zien en te spreken. De onderzoekers werd gevraagd een score te geven ten aanzien van de mate van verbetering. Bij ouders werd een interview afgenomen gericht op de verandering van ADHD symptomen in de tijd. Daarnaast werden leerkrachten verzocht vragenlijsten in te vullen die gericht waren op gedrag en ADHD symptomen. Na 8 weken bleken de kinderen in de atomoxetine groep significant minder last te hebben van ADHD symptomen dan de kinderen in de placebogroep. De ouders vermeldden een duidelijke verbetering op alle ADHD symptomen. De leerkrachten zagen vooral een verbetering voor wat betreft de hyperactiviteit. De onderzoekers zagen eveneens een verbetering, maar waren bescheiden in het toekennen van de mate van verbetering. In het algemeen werd atomoxetine goed verdragen door de deelnemende kinderen.

Vergeleken met kinderen met alleen ADHD hebben we geconstateerd dat de mate van verbetering van ADHD symptomen, die we vonden geringer is dan de verbetering die gevonden is in eerdere studies met atomoxetine bij kinderen met alleen ADHD. Ook zagen we vooral een effect op het hyperactieve en impulsieve gedrag en was het effect op de concentratie, hoewel nog steeds erg goed, minder uitgesproken. Atomoxetine werkt bij kinderen met alleen ADHD even goed op hyperactiviteit/impulsiviteit als op concentratie. De bijwerkingen die spontaan gerapporteerd werden, waren niet anders dan de bijwerkingen die al bekend waren uit onderzoek bij kinderen met alleen ADHD. Wel vonden we in verhouding iets vaker bijwerkingen en werden de bijwerkingen als ernstiger geduid dan bij kinderen met alleen ADHD. Onze bevindingen dat het medicijn iets minder effectief is dan bij kinderen met alleen ADHD en dat deze kinderen gevoeliger zijn voor bijwerkingen komen overeen met de bevindingen van de RUPP (een onderzoeksgroep in de Verenigde Staten) die in 2005 een vergelijkbare studie hebben gepubliceerd waarbij kinderen met ASS en ADHD symptomen methylfenidaat voorgeschreven hebben gekregen.

We kunnen op basis van ons onderzoek stellen dat atomoxetine effectief is als behandeling van ADHD symptomen bij kinderen met ASS, dat het effect in eerste instantie optreedt in vermindering van de hyperactiviteit en dat het medicijn goed verdragen wordt.

Na deze eerste 8 weken hebben 88 kinderen deelgenomen aan de 20 weken open label fase dat wil zeggen dat alle kinderen, ouders en onderzoekers op de hoogte waren van het feit dat er behandeld werd met atomoxetine. Zoals gezegd heeft niemand van hen geweten wat zij in de eerste 8 weken hebben ingenomen. In totaal hebben 73 kinderen dit onderdeel afgerond. Tijdens deze fase werden de kinderen regelmatig gezien, beantwoordden vragen en deden een aantal testen. De ouders werden op regelmatige tijden geïnterviewd. We hebben onderzocht wat het effect van atomoxetine op de langere termijn op ADHD symptomen is, of het middel goed werd verdragen en wat er met bijwerkingen gebeurde in de loop der tijd. De opzet en resultaten van zijn beschreven in *hoofdstuk 3* van dit proefschrift. We zagen dat er in de loop der tijd sprake is van een continue verbetering van alle ADHD symptomen, waarbij we na 20 weken nog geen eind aan deze verbetering zagen. Ook zagen we dat de verbetering op de concentratie in de loop der tijd gelijk werd aan de verbetering op de hyperactiviteit en impulsiviteit. Dit in tegenstelling tot kinderen met alleen ADHD, waarbij na 3 maanden behandeling met atomoxetine geen verdere verbetering wordt beschreven. De meest voorkomende bijwerkingen waren dezelfde die gezien worden bij kinderen met alleen ADHD, namelijk misselijkheid, buikpijn, verminderde eetlust en moeheid. We zagen dat de bijwerkingen in de loop der tijd afnamen of zelfs verdwenen, vooral misselijkheid en

moeheid. De belangrijkste beperking in deze fase van de studie was het feit dat iedereen wist dat de kinderen behandeld werden met atomoxetine, waarbij men dus meer alert is op verbetering en bijwerkingen, zodat de bevindingen niet objectief zijn.

Samenvattend kunnen we zeggen dat het tot een half jaar kan duren tot het volledige effect van atomoxetine op ADHD symptomen bij kinderen met een ASS is bereikt. We weten nu ook dat bijwerkingen van atomoxetine bij kinderen met ASS en ADHD symptomen in frequentie en ernst afnemen in de loop der tijd.

In *hoofdstuk 4* wordt het effect van atomoxetine op twee neuropsychologische taken beschreven waaruit bleek dat de kinderen met een ASS en ADHD symptomen die behandeld werden met atomoxetine beter in staat waren hun impulsen te remmen/ controleren (inhibitie taak), maar niet beter in staat waren irrelevante informatie buiten te sluiten (interference taak). De kinderen die een goed resultaat lieten zien op de inhibitie taak, waren echter niet dezelfde kinderen zijn die een verbetering van de klinische ADHD symptomen lieten zien. Er was dus geen samenhang in het verbeteren van de ADHD symptomen en een verbetering in inhibitie (remming). Deze bevinding kan betekenen dat er verschillende oorzaken zijn die leiden tot ADHD symptomen ofwel problemen in de inhibitie bij kinderen met een ASS en ADHD symptomen. Het betekent ook dat deze taak slechts een beperkte waarde heeft om het klinische effect van atomoxetine op ADHD symptomen bij kinderen met een ASS te monitoren.

Uiteraard waren we ook benieuwd of behandeling met atomoxetine effect zou hebben op de kernsymptomen van ASS, zoals communicatie, wederkerigheid in het contact en het verwerken van sociale informatie. Ouders hebben voorafgaande aan de start van de studie en gedurende de studie op vaste tijden vragenlijsten ingevuld die vragen naar (sociaal) gedrag. In *hoofdstuk 5* zijn de uitkomsten en resultaten beschreven. We zagen geen effect op de kernsymptomen die horen bij een ASS, wel zagen we veranderingen op een aantal subschalen, namelijk hyperactiviteit, onaangepaste spraak, stereotiep gedrag en angst voor veranderingen. We weten niet precies hoe we deze veranderingen kunnen verklaren. De vraag is of het echt veranderingen zijn in sociaal gedrag of veranderingen in gedrag tengevolge van de afname van ADHD symptomen. Voor wat betreft hyperactiviteit is dat duidelijk. Eén van de items van onaangepaste spraak is oeverloos praten, hetgeen ook als een ADHD symptoom kan worden gezien. Toch zijn deze veranderingen interessant, temeer daar ze ook gevonden zijn in een aantal kleinere studies met atomoxetine. Het is belangrijk in de toekomst onderzoek te doen naar sociaal gedrag met specifieke meetinstrumenten, waarbij gebruik wordt gemaakt van meerdere bronnen zoals ouders, leerkrachten en onderzoekers.

Tevens waren we benieuwd naar voorspellende factoren. Welke kinderen met een ASS en ADHD symptomen profiteren het beste van behandeling met atomoxetine? Zijn dat kinderen die nooit eerder medicatie hebben gebruikt, jongens of meisjes, kinderen met een autische stoornis of kinderen met PDDNOS, etc.? In *hoofdstuk 6* worden de antwoorden op deze vragen gegeven. We vonden geen voorspellende factoren. Wel konden we aantonen dat kinderen met een ASS en ADHD symptomen ook nog na 5 weken behandeling met atomoxetine kunnen gaan reageren op deze behandeling dat wil zeggen dat een negatieve bevinding na 5 weken behandeling niets zegt over het uiteindelijke resultaat, in tegenstelling tot kinderen met alleen ADHD, waarbij bekend is dat de kans op een positief effect vrijwel nihil is als er na 5 weken behandeling met atomoxetine geen enkele verandering is waargenomen. Deze bevinding is in lijn met de resultaten zoals beschreven in *hoofdstuk 3* waarin we stelden dat kinderen met een ASS en ADHD symptomen tijd nodig hebben om te reageren op de behandeling met atomoxetine.

Betekenis van de bevindingen

Onze studie heeft aangetoond dat behandeling met atomoxetine van ADHD symptomen bij kinderen met een ASS een zinvolle behandeling is. De ADHD symptomen verminderen in ernst en het medicijn wordt goed verdragen. We vonden een duidelijke verbetering van de ADHD symptomen op alle terreinen, waarbij het effect op de hyperactiviteit en impulsiviteit in eerste instantie het grootste is en het effect op concentratie daarna volgt om uiteindelijk even groot te zijn als effect op de hyperactiviteit en impulsiviteit. Tevens vonden we kleine verbeteringen in sociaal gedrag als het gaat om onaangepaste spraak, stereotiep gedrag en minder angst voor veranderingen.

We hebben tevens aangetoond dat het geduld vraagt om kinderen met een ASS en ADHD symptomen te behandelen. Een eventueel effect kan voor het eerst optreden nadat 5 weken behandeling is geboden en een optimaal effect kan ook nog bereikt worden tot 6 maanden behandeling.

We weten nu ook dat behandeling met atomoxetine goed wordt verdragen door kinderen met een ASS en dat eventuele bijwerkingen in de loop der tijd afnemen.

Toekomstig onderzoek

Atomoxetine lijkt een goede medicamenteuze behandeling als het gaat om de behandeling van ADHD symptomen bij kinderen met een ASS. Er zijn echter inclusief het in dit proefschrift beschreven onderzoek maar twee dubbel blind placebo gecontroleerde studies (RCT's) gedaan. Bij de eerste studie was het aantal deelnemers klein en mocht behalve atomoxetine ook andere medicatie worden ingenomen. De RADAR studie was groter en kinderen hebben alleen atomoxetine ingenomen, maar wij vertrouwden vooral

op observaties van ouders. Meer goed opgezette RCT's waarbij consequent gebruik wordt gemaakt van meerdere informatiebronnen zoals kinderen zelf, ouders, leerkrachten en onderzoekers is te adviseren.

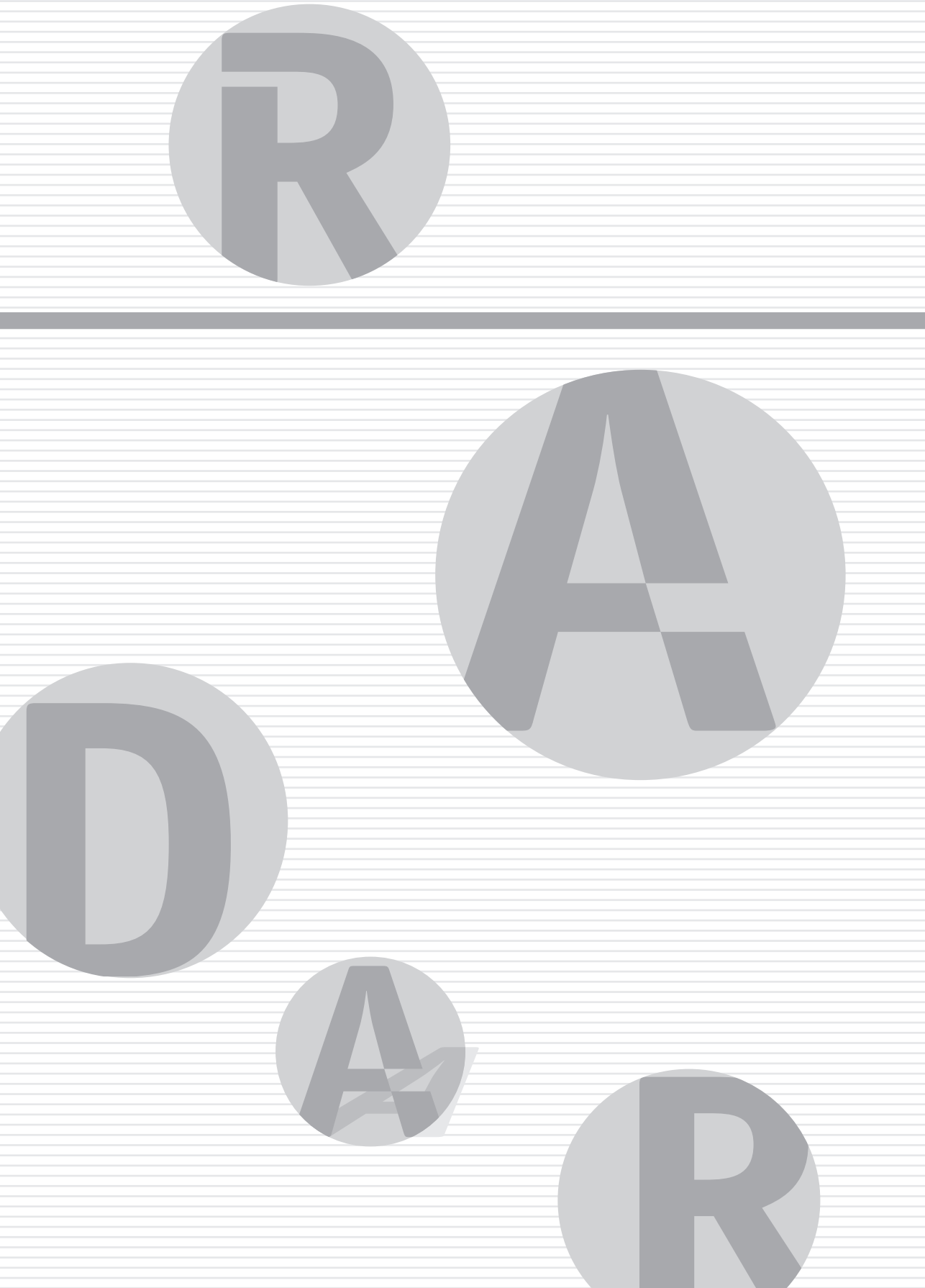
We hebben een aantal verschillen in reactie op atomoxetine gevonden tussen kinderen met ASS en ADHD symptomen en kinderen met alleen ADHD. Kinderen met zowel ASS als ADHD symptomen hadden een minder groot effect op behandeling, reageerden in eerste instantie vooral met een verbetering op hyperactief/impulsief gedrag, waren gevoeliger voor bijwerkingen en hadden (als groep) meer tijd nodig voordat verbetering zichtbaar werd. We weten niet goed hoe we deze verschillen moeten verklaren. Het zou kunnen zijn dat kinderen met beide aandoeningen sowieso een kwetsbaarder brein hebben of dat verschillende pathofysiologische aspecten een rol spelen. Het is belangrijk meer onderzoek te doen op dit gebied.

Het zou zo kunnen zijn dat kinderen met ASS meer baat hebben bij andere doseringen van atomoxetine, zoals een hogere dagdosis, een lagere dagdosis, een verdeling van de dosis over de dag heen en/of een langzamere opbouw van de dosering. Toekomstig onderzoek kan hier rekening mee houden en dit nader onderzoeken.

Aangezien op dit moment behandeling met psychostimulantia, zoals methylfenidaat, eerste keus behandeling is van ADHD symptomen en de RUPP studie in grote lijnen dezelfde bevindingen heeft als wij in onze RADAR studie zou het interessant zijn een vergelijkende, bij voorkeur dubbel blinde, studie op te zetten waarbij behandeling van ADHD symptomen bij kinderen met een ASS door atomoxetine, methylfenidaat en een placebo rechtstreeks met elkaar worden vergeleken.

In onze studie vonden we enige verbetering op het gebied van stereotiep gedrag en angst voor veranderingen. Deze (milde) verbeteringen zijn ook beschreven in een aantal andere atomoxetine onderzoeken bij kinderen met ASS en ADHD symptomen, zodat het aan te bevelen is een studie op te zetten die speciaal ontworpen is om het effect van atomoxetine op sociaal gedrag bij kinderen met een ASS te onderzoeken.

Tot slot is het raadzaam om onderzoek te doen naar de veronderstelling dat kinderen met een ASS en ADHD symptomen meer zullen profiteren van aangeboden lesstof en gedragstherapie, als zij goed reageren op behandeling met medicatie, zoals atomoxetine.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Dankwoord

Dankwoord

Het is af! Ruim tien jaar geleden was in Zwolle een bijeenkomst om te brainstormen over een placebo gecontroleerde studie met atomoxetine bij kinderen met een Autisme Spectrum Stoornis in navolging van een pilot studie die mijn collega Pieter Troost in Groningen had uitgevoerd. Deze brainstorm bijeenkomst heeft geleid tot het opzetten van de RADAR studie en uiteindelijk tot het schrijven van dit proefschrift. Het was een avontuur met pieken en dalen, met hollen en stilstaan, waar ik nu opgelucht en met trots op terug kan kijken. Het proefschrift ligt er met 5 gepubliceerde artikelen in mooie tijdschriften, wat niet gelukt was zonder de hulp van heel veel mensen die mij geholpen hebben met praktische zaken, steun, complimenten en geduld.

Heel veel dank gaat uit naar de 97 kinderen en jongeren en hun ouders die hebben deelgenomen aan de studie. Zonder hun deelname, enthousiasme en uithoudingsvermogen was dit onderzoek er niet geweest. Het was mooi om te zien hoe betrokken en gemotiveerd zij deelnamen en hoe nieuwsgierig ook zij waren naar de effecten van atomoxetine op hun symptomen. De 97 deelnemers (en hun ouders), die hebben deelgenomen aan de studie zouden er niet geweest zijn zonder de negen deelnemende centra in Nederland. Ik ben hen zeer erkentelijk.

Veel dank aan mijn twee promotoren Prof. dr. P.J. Hoekstra en Prof. dr. J.K. Buitelaar. Beste Pieter; Ik heb veel bewondering voor jouw snelheid van denken, jouw vermogen te analyseren, jouw prachtige schrijfstijl en je enorme kennis van zaken. Het is fantastisch om te zien hoe jij ingewikkelde materie in een paar trefzekere zinnen begrijpelijk uit kunt leggen en op kunt schrijven. Je komt bijzonder snel tot de kern. Ik was erg blij met jouw niet aflatende geduld om steeds opnieuw met mij de statistiek door te nemen. Ik heb goede herinneringen aan de dagen dat we er letterlijk samen voor zaten, waar behalve tijd voor hard werken ook tijd was voor humor en gezelligheid. Beste Jan; De artikelen zijn zo goed geworden als ze zijn met dank aan jouw frisse, kritische blik en suggesties voor verbetering. Je reageerde per mail altijd direct op onze vragen en dat voelde als heel betrokken en prettig.

Aan de wieg van dit traject stond Prof. dr. R.B. Minderaa, die mij de kans heeft gegeven tijdens mijn werk bij Accare te starten met dit onderzoek. Beste Ruud; dankjewel voor deze kans, de steun en de ruimte die ik van jou heb gekregen. Inmiddels geniet je van een welverdiend pensioen en het goede leven in Spanje.

De studie is gecoördineerd door Eli Lilly, waar heel veel mensen werken en ook veel mensen door de jaren heen betrokken zijn geweest bij deze studie. Twee mensen wil

ik speciaal bedanken; Simone Knijff en Nicole Dieteren. Beste Simone; al in Zwolle was jij erbij. Jouw rol bij het opzetten van deze studie, waar negen centra in Nederland aan deelnamen was enorm belangrijk. Je was sparringpartner, schreef allerlei partijen aan, coördineerde de logistiek, was verbindend en deed dat op een hartelijke, enthousiaste en laagdrempelige manier. Beste Nicole; jij bent jarenlang met mij opgetrokken in dit avontuur. Aanvankelijk als uitvoerder en verbindende partij tussen de 9 centra en na het vertrek van Simone als verantwoordelijke voor de studie vanuit Eli Lilly. De samenwerking was altijd plezierig, prettig en waardevol.

In Groningen hadden we niet zoveel kinderen kunnen includeren zonder Harma Moorlag. Beste Harma, heel veel dank voor de organisatie van de studie binnen Accare, die op rolletjes liep en tot in detailniveau klopte. Ook de andere centra hebben gebruik van jouw kennis en kunde mogen maken. Nijmegen was op meerdere manieren en met veel mensen betrokken bij deze studie, waaronder Gigi van de Loo, Jolanda van der Meer en Rutger Jan van der Gaag. Beste Gigi; heel veel dank voor het includeren van een derde van de kinderen en het meelezen en meedenken tijdens het schrijven van de artikelen. Beste Jolanda; we zijn een onderdeel van elkaars proefschrift geworden en hebben vooral via de mail goed contact gehad. Ik heb bewondering voor jouw onderdeel in deze studie; het analyseren en opschrijven van het neuropsychologische deel van onze studie. Beste Rutger Jan; veel dank voor de oprechte belangstelling en je vriendelijke stimuleren als we elkaar troffen, dat heeft me altijd goed gedaan. Vanuit Utrecht was Bertine Lahuis vanaf de allereerste bijeenkomst betrokken. Beste Bertine; veel dank voor het meedenken, het includeren van kinderen, en het delen van de bijzondere ervaring van het doen van onderzoek en het schrijven van een proefschrift in combinatie met patiëntenzorg, beleid en thuis. In Breda was Alma Weber bijzonder actief en ik heb genoten van haar humor, vrolijkheid, optimisme en enthousiasme. In Hoorn was Jaap Hage op zijn vriendelijke, bescheiden wijze de trekker van het onderzoek. Helaas is hij overleden en heeft de afronding niet mee mogen maken. Het was leuk Andries Korebrits weer te ontmoeten, die ik nog kende uit onze studietijd in Utrecht. Het was een eer Frits Boer te ontmoeten, die vanuit Amsterdam actief was.

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De leden van de leescommissie Prof. dr. O.M. Tucha, Prof. dr. A. Popma en Prof. dr.

R.R.J.M. Vermeiren wil ik bedanken voor het lezen en beoordelen van het proefschrift.

Dit proefschrift was er niet geweest zonder de belangstelling van familie, vrienden en collega's. Steeds opnieuw gaven zij mij het zetje in de rug dat ik nodig had om mijzelf in stilte terug te trekken zodat ik me kon wijden aan het verwerken van de data en het schrijven van dit proefschrift.

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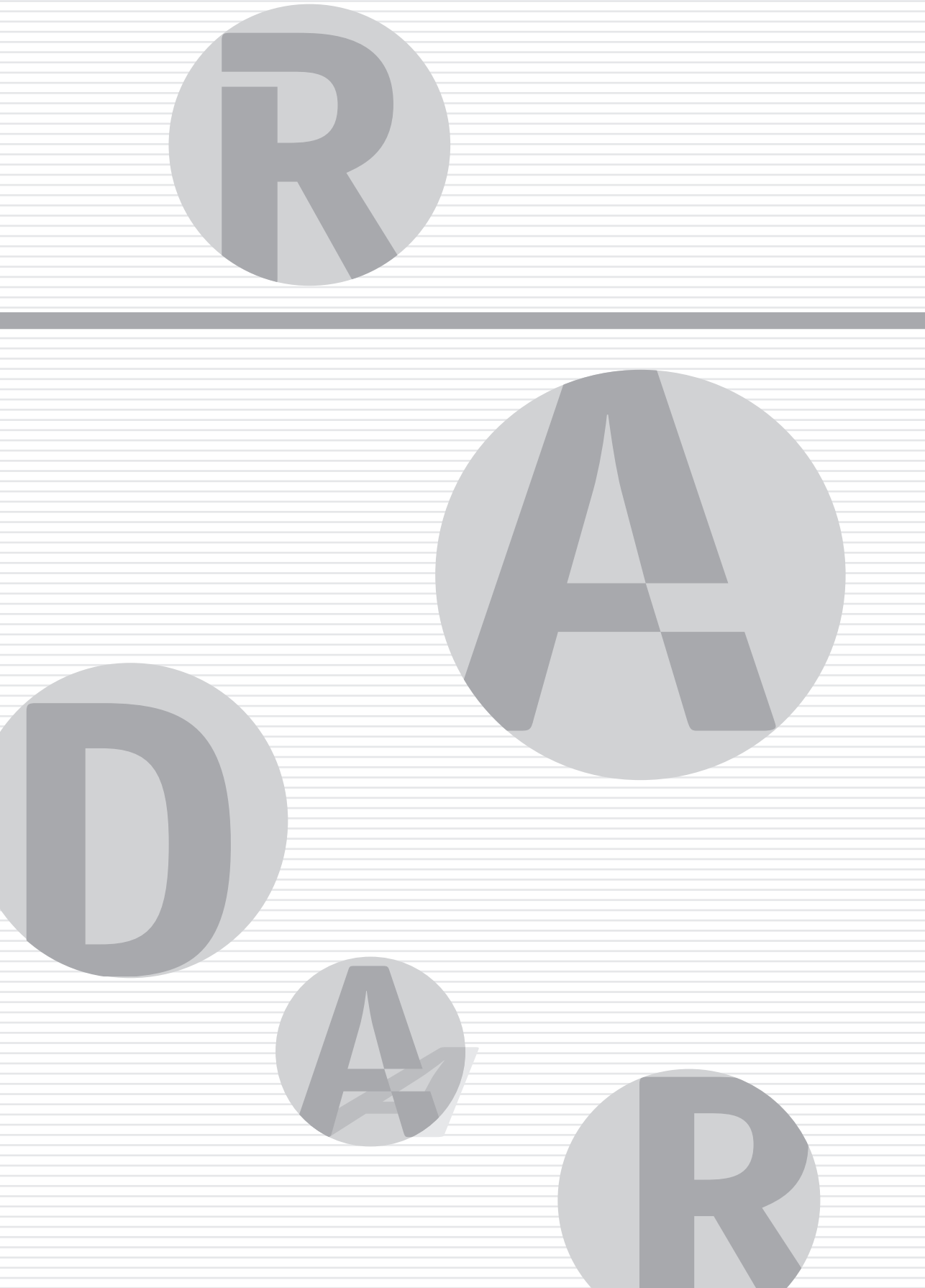
Lieve Rixt en Jelle; wat bof ik met jullie als mijn kinderen! Ik ben apetrots en vol bewondering hoe jullie school, werk, vrienden en huiswerk maken combineren en genieten van het leven; daar heb ik een goed voorbeeld aan gehad.

Lieve Corstiaan, de liefste man die er is, mijn maatje en beste vriend; wij zeilen verder!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Curriculum Vitae

Curriculum Vitae

Myriam Harfterkamp werd op 30 april 1965 geboren in Borculo. Ze behaalde haar VWO diploma in 1983 aan de Rooms Katholieke Scholengemeenschap Marianum in Groenlo. Aansluitend studeerde zij geneeskunde aan de Rijksuniversiteit Utrecht waar zij in 1991 voor haar artsexamen slaagde.

Na verschillende banen als basisarts bij de RIAGG Zwolle, de RIAGG Stad Utrecht en psychotherapeutische gemeenschap "de Bosrand" in Dennenoord Zuidlaren werd zij in 1994 aangenomen voor de opleiding tot psychiater. Zij begon in 1995 bij de RIAGG Friesland met haar stage sociale psychiatrie (opleider G.J. van Doggenaar), vervolgens haar keuzejaar kinder- en jeugdpsychiatrie bij het Universitair Centrum Kinder- en Jeugdpsychiatrie (UCKJP; opleider R.B. Minderaa) en daarna de basisopleiding tot psychiater bij de GGZ Groningen (opleider C.F.A. Milders). In 2000 keerde zij terug naar het UCKJP dat onderdeel van Accare werd voor haar aantekeningsjaar kinder- en jeugdpsychiatrie. Na het behalen van de aantekening voor kinder- en jeugdpsychiater heeft zij aanvankelijk twee banen gecombineerd, namelijk bij de GGZ Groningen, locatie Winschoten en bij het UCKJP in Groningen. In 2002 is zij helemaal overgestapt naar het UCKJP van Accare.

Bij Accare heeft Myriam tot 2007 als staflid op de polikliniek gewerkt en van 2007 tot 2014 als kinder- en jeugdpsychiater en Hoofd Behandelzaken van de kliniek voor kinderpsychiatrie. In 2005 is zij naast haar werk op de polikliniek gestart met dit onderzoek en vervolgens is zij klinisch werk en wetenschappelijk onderzoek blijven combineren, hetgeen geleid het tot het afronden van dit proefschrift.

In 2014 is Myriam bij het Universitair Centrum Psychiatrie (UCP) van het UMCG gaan werken als psychiater van de open opname afdeling en als Hoofd Behandelzaken van de afdeling Intensieve Psychiatrie. Sinds augustus 2015 is zij tevens Chef de Clinique en maakt deel uit van het Dagelijks Bestuur van het UCP.