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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); ~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 (Gadow et al. 2006; Holtmann et al. 2007). Although a combination of these diagnoses was precluded by the text revision of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), the fifth edition (DSM-V) has now made it possible to classify both disorders at the same time (American Psychiatric Association 2000, 2013).

Several small-scale, mostly open-label studies (Jou et al. 2005; Arnold et al. 2006; Posey et al. 2006; Troost et al. 2006; Charnsil 2011; Zeiner et al. 2011; 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 have demonstrated superior efficacy of atomoxetine compared with 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 a meta-regression analysis have 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 al. 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 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 United States 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 1–3 weeks of 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 from our double-blind placebo-controlled 8 week trial, which was followed by an open-label 20 week extension period.

Study Design and 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 8 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 had received 20 weeks of treatment with atomoxetine. For

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TABLE 1. RESULTS OF REPEATED MEASURES ANOVA WITH THE ADHD-RS TOTAL SCORE AT BASELINE AND AT WEEK 8 AS THE REPEATED OUTCOME MEASURE IN PARTICIPANTS WITH COMPLETE DATA AFTER 8 WEEKS OF TREATMENT WITH ATOMOXETINE

Predictor	Demographics	p value	η^2
Male sex, <i>n</i> (%)	75 (87.2)	0.19	0.02
Age, mean (SD) in years	9.96 (2.83)	0.77	0.10
IQ, mean (SD)	92.6 (17.1)	0.16	0.66
Previous psychopharmacological treatment, <i>n</i> (%)	53 (61.6)	0.28	0.01
CYP2D6 genotype, <i>n</i> (%) ^a		0.98	0.001
• Poor	10 (11.6)		
• Intermediate	24 (27.9)		
• Extensive	51 (59.3)		
• Ultra-rapid	0 (0)		
Type of ASD, <i>n</i> (%)		0.17	0.02
• PDD-NOS/Asperger's disorder	35 (40.7)		
• Autistic disorder	51 (59.3)		

^aOne missing genotype.

ADHD-RS, Attention-Deficit/Hyperactivity Disorder Rating Scale; IQ, intelligence quotient; ASD, autism spectrum disorder; PDD-NOS, pervasive developmental disorder-not otherwise specified.

both groups, we had assessments at baseline and after 5 and 8 weeks of treatment.

Participants had to be between 6 and 17 years of age, have an intelligence quotient (IQ) ≥ 60 , and 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 al. 2003) above the cutoff; ADHD diagnoses had to meet DSM-IV-TR criteria A–D for ADHD any type. Exclusion criteria included a weight of < 20 kg; presence of psychosis, bipolar disorder, or substance abuse; a serious medical illness; history of seizures; ongoing use of psychoactive medications other than the study drug; and intended start of a structured psychotherapy or inpatient treatment.

Parents and children ≥ 12 years of age all provided written informed consent, and younger children gave 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 over the past week to be scored on a four point scale. The total score is the sum of the scores on each of the 18 items (Du Paul et al. 1998).

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

Data Analysis

We combined all patients into one group; for the group originally allocated to atomoxetine 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 who had completed the first 8 weeks of the open-label extension period ($n = 43$) we considered 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 [PDD], such as Asperger's disorder and pervasive developmental disorder not otherwise specified [PDDNOS]). A *p* value of 0.05 for the time by predictor term was considered evidence of a moderating effect of the predictor on treatment.

We additionally investigated whether an early response to treatment predicted the further treatment course. In line with Newcorn et al. (2009), we defined early response as a $\geq 25\%$ 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 ($p = 0.004$). Within-group analyses revealed that participants with an early response after 5 weeks remained stable during 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 week 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), in which none of these factors were associated with treatment response either (Newcorn et al. 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 al. 2007), which we did not observe.

Previous studies had also suggested that treatment-naïve children and adolescents with ADHD have a 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. It is of note that 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 12 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 response after the first 5 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). Therefore, 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 that there is a lack of response.

The most important limitation of the present study is its modest sample size, even though 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 would 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.

Disclosures

Myriam Harfterkamp has accepted invitations for congress travels from Eli Lilly and Eurocept. D. Van der Meer has no financial disclosures. Ruud B. Minderaa was an advisor for Eli Lilly. Jan K. Buitelaar has been a consultant to/member of advisory board of/and/or speaker for Bristol-Myer Squibb, Eli Lilly, Janssen Cilag BV, Medice, Organon/Shering Plough, Servier, Shire, and UCB. Gigi van de Loo-Neus has received honoraria for a presentation from Eli Lilly and was member of the advisory board for Shire and UCB Pharma B.V. Pieter J. Hoekstra has received honoraria for presentations or advice from Desitin, Eli Lilly, and Shire. Data analyses were conducted by Dennis van der Meer, Myriam Harfterkamp and Pieter J. Hoekstra.

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