International Journal of Neuropsychopharmacology, 2015, 1–5

doi:10.1093/ijnp/pyv044
Brief Report

BRIEF REPORT

# Effect of Atomoxetine on the Cognitive Functions in Treatment of Attention Deficit Hyperactivity Disorder in Children with Congenital Hypothyroidism: A Pilot Study

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## Abstract

**Background:** With early initiation of thyroxine supplementation, children with congenital hypothyroidism (CH) retain some subtle deficits, such as attention and inhibitory control problems. This study assessed the effects of atomoxetine on cognitive functions in treatment of attention deficit hyperactivity disorder (ADHD) symptoms in children with CH.
**Methods:** In a 6-month, open-labeled pilot study, 12 children were recruited and received atomoxetine. The measures of efficacy were scores on the Swanson, Nolan and Pelham Teacher and Parent Rating Scale, version IV (SNAP-IV) and Clinical Global Impression-Severity scale (CGI-S). The cognitive functions were evaluated with the Wechsler Intelligence Scale for Chinese Children, Digit Span, Wisconsin Card Sorting Test, and Stroop test.
**Results:** A statistically significant difference was found between the mean CGI-S and SNAP-IV scores before and after treatment ($p < 0.01$). All the indicators of cognitive functions at the endpoint were improved compared with those at baseline. No serious adverse events were reported.
**Conclusion:** Atomoxetine appears to be useful in improving ADHD symptoms, as well as cognitive functions, in children with CH. Larger, randomized, double-blinded, clinical trials are required to replicate these results.

**Keywords:** ADHD, atomoxetine, attention deficit hyperactivity disorder, CH, cognitive functions, congenital hypothyroidism

## Introduction

Congenital hypothyroidism (CH) is a condition of insufficient production of a thyroid hormone, which is due to thyroid dysgenesis or thyroid dyshormonogenesis. It results in irreversible damage of the central nervous system (Porterfield, 1994), presenting serious mental and motor retardation (Simic et al., 2009). Neonatal CH screening and early replacement therapy of thyroxine has been highly effective in preventing retardation (Maitusong et al., 2012).

By raising the intelligent quotient (IQ) to within normal range in subjects with CH, the individuals gain a higher quality of life and better cognitive functions. However, accumulating evidence suggests that, even though their performance is definitely improved by earlier initiation of thyroxine supplementation, children with CH still have some subtle cognitive and motor deficits (Fuggle et al., 1991; Bargagna et al., 2000; Rovet and Ehrlich, 2000), such as attention deficit and inhibitory control problems. Rovet (1999)

**Received:** December 6, 2014; **Revised:** March 26, 2015; **Accepted:** April 13, 2015

reported that adolescents with CH had poorer attention compared with matched controls. Other studies found similar results in children, adolescents, and young adults (Kooistra et al., 2001; Song et al., 2001). Alvarez and colleagues (2010) also showed that inhibitory control was significantly lower in children with CH than in controls. All the results indicate that subjects with CH have a higher possibility of attention deficit hyperactivity disorder (ADHD) symptoms.

ADHD is characterized by age-inappropriate inattention, hyperactivity-impulsivity, or both, which play an important role in the impairment of academic and social function for school-aged children. ADHD combined with CH would have more negative influences on the children. However, the multiplicity of the both conditions make the treatment challenging.

To the best of our knowledge, there is no clinical trial to explore the treatment of children with both ADHD and CH. Atomoxetine is a selective norepinephrine reuptake inhibitor approved for the treatment of ADHD. In the present pilot study, our aim was to evaluate the efficacy and tolerability of atomoxetine on ADHD symptoms and cognitive functions in children with CH.

## Methods

### Study Design and Subjects

In this pilot study, we evaluate the effects of 6-month atomoxetine treatment on ADHD symptoms and cognitive functions in children with CH. The participants were recruited from an outpatient clinic. Those children with CH who were suspected of having ADHD symptoms were administered structured interviews in order to assess ADHD symptomatology. Children included in this study met ADHD criteria according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, under the following three subtypes: ADHD inattentive type, ADHD hyperactive-impulsive type, and ADHD combined type. All the patients were evaluated with the Swanson, Nolan and Pelham Teacher and Parent Rating Scale, version IV (SNAP-IV) and Clinical Global Impression-Severity scale (CGI-S), both scales of ADHD symptoms, at baseline and at 6 weeks, 12 weeks, and/or 6 months after starting atomoxetine treatment. Tests of cognitive functions, including the Wechsler Intelligence Scale for Chinese Children (WISC-R),, Digit span, Wisconsin Card Sorting Test (WCST), and Stroop color-word test, were evaluated at baseline and endpoint. Thirteen gender- and age-matched children (11 boys and 2 girls) without ADHD from a primary school voluntarily took part into the study as normal controls.

Exclusion criteria for the study were: (a) IQ under 70; (b) a psychiatric diagnosis with significant symptoms (psychosis, autism, depression, anxiety, mood disorder) or taking psychoactive medications; (c) a history of significant traumatic brain injury; (d) sensorimotor handicaps (paralysis, deafness, blindness); or (e) serious somatic disorders, such as cardiovascular diseases, serious gastrointestinal stenosis, dysphagia, etc.

The study procedures were explained to children and parents, and consents were obtained from the children and their families. The study protocol was approved by the Institutional Review Board of the Children's Hospital, Zhejiang University School of Medicine.

### Measures for ADHD Symptoms and Cognitive Functions

The children were assessed by a trained multidisciplinary ADHD diagnostic team with a comprehensive assessment process, including physical examination, electroencephalogram and electrocardiograph (ECG).

ADHD symptoms were assessed with the SNAP-IV (18 item) and CGI-S (Wu, 1984). The CGI-S is a 7-point scale (1 = not at all ill, 7 = maximal impairment).

We employed the WISC-R, Digit Span, WCST, and Stroop color-word test to evaluate the cognitive functions. The WISC-R is one of the most-used standardized tests of IQ. The test consists of 12 subtests, and three IQ scores can be yielded: full scale (FIQ), verbal (VIQ), and performance (PIQ). The Chinese version of the WISC-R has good reliability and validity (Lin and Zhang, 1986; Zhang et al., 2011), which was employed to assess the cognitive abilities in the present study. The Digit Span is used to evaluate verbal working memory, immediate recall, and the ability to hold, retain, and manipulate new verbal information (Groth-Marnat and Baker, 2003), which is a subtest of WISC-R (Lin and Zhang, 1986). Participants are read a string of numbers and asked to repeat them in the same order and backward. The total score ranges from 0 to 30. The WCST (Tsuchiya et al., 2005) measures the ability to form abstract concepts, to sustain attention, and to shift cognitive set flexibility in response to changing conceptual rules while inhibiting inappropriate responses. It is one of the most common tests for executive function in the school-aged population (Ozonoff, 1995; Schmitz et al., 2002). Children were requested to match those cards with additional cards under changing rules (including matching the shapes, different colors, quantity, and designs). The number of right and Wrong matches and the time children took to learn new rules, as well as the mistakes, were measured. The Stroop color-word test (Stroop, 1935; Ji and Jiao, 1987; Golden and Golden, 2002) has been widely used to assess the executive functions of cognitive inhibition and selective attention. It includes four tasks: word reading, color reading, word reading of colored words, and color naming of colored words (Hong et al., 2010). The completion times and the number of errors made during each task/test were recorded.

### Medication Dosage

The patients received atomoxetine (Strattera, Eli Lilly and Company) at 0.5 mg/kg/day for the first week, and then doses increased to 1.2 mg/kg/day. Atomoxetine was given orally once daily as 10, 25, and 40 mg capsules, with the doses adjusted to achieve the body-weight target dose.

### Clinical Safety Evaluation

Clinical safety was indicated by means of the child's and parents' reports of adverse events, the ECG, and laboratory tests of thyroid and liver functions.

### Data Analysis

Data were entered into Excel software and analyzed in the SPSS (version 13.0) software package. Analyses were conducted using one-way analyses of variance (ANOVAs) with repeated measures to compare mean scores at baseline to scores at different time of post treatment. The t-test was used to compare the cognitive functions between the time of baseline and that of the endpoint (Month 6). We used last observation carried forward in our analyses of missing data. A $p$-value of less than 0.05 was regarded as statistically significant for all statistical tests.

## Results

Of the 26 children initially assessed, 12 did not meet ADHD criteria and 2 children and their parents refused to participate the study. Finally, 12 children went into this pilot study. Of them, 10

were males (83.3%) and 2 were females (16.7%). The mean age was 8.7 years old, with a standard deviation of 2.1 (6.5–11 years).

Among these children, 11 of them were diagnosed with CH by neonatal screening before they were 1 month old, and one was diagnosed with CH when he had developmental delay symptoms at 18 months of age. All were administered with levothyroxine (Euthyrox, Merck KGaA) replacement, presently with a dosage of 6.9±2.7 μg/kg/day. Ultrasound scanning suggested dysgenesis of thyroid tissue (six cases), ectopic thyroid tissue (two cases), and normal locations with generally normal sizes of thyroid glands (four cases). This group of samples consisted of two children with an inattentive subtype, four children with a hyperactive-impulsive subtype, and six children with the combined subtype.

Thirteen children of normal controls were recruited from a local school with similar demographic characteristics to the CH group. All of them were in primary school with a mean age of 8.3 years (standard deviation [SD] = 1.6). There were no statistical differences found for mean age and gender proportion between these two groups (t = 0.348, $p = 0.731$ for mean age, and $X^2 = 0.008$, $p = 0.93$ for gender proportion).

### Medications Dosages and Safety

All the patients reached the target dose range with an average of 1.1 mg/kg/day (0.8–1.3) of atomoxetine in 2–4 weeks. The dosage of levothyroxine remained the same, according to weight adjustment. Thyroid functions and liver function were detected along with the evaluation of SNAP-IV, and were all in normal ranges (Table 1).

Three patients reported adverse events (25%) with the administration of atomoxetine, including a decrease in appetite (n = 2) and abdominal pain (n = 1). The blood tests of thyroid functions and liver function were in normal range after atomoxetine treatment.

### Response to Treatment

The mean baseline score of the parents' version of SNAP-IV was 33.8 (SD = 4.9). Post-treatment scores at week 6, week 12, and month 6 reduced to 27.3 (SD = 4.7), 22.4 (SD = 4.3), and 17.5 (SD = 3.7), respectively (Table 1). The mean baseline score of the teacher version of SNAP-IV was 34.3 (SD = 5.5). Post-treatment scores at week 6, week 12, and month 6 reduced to 27.8 (SD = 4.9), 21.0 (SD = 3.1), and 17.2 (SD = 3.1), respectively (Table 1). Significant decreases of SNAP-IV scores were observed for both parent and teacher versions over baseline to month 6. Repeated measures ANOVAs revealed these statistical differences: F = 131.5, $p < 0.01$ for parent ratings, and F = 98.7, $p < 0.01$ for teacher ratings.

### Changes of Cognitive Functions

After 6 months of atomoxetine treatment, children with CH and ADHD showed significant improvement in FIQ ($p = 0.002$) and PIQ ($p = 0.011$), and a non-significant improvement trend in VIQ (from 97.5 to 99.5; $p = 0.239$). On the other hand, there were no significant changes found for WISC-R over 6 months in normal controls (Table 2).

For the Digit Span, t-tests revealed that children treated with atomoxetine performed better at month 6 than at baseline. Improvement in a subtest of a backward task was found, but was not significant ($p = 0.067$).

Compared with baseline, the improvement of WCST for children treated with atomoxetine at month 6 was significant in 12 of the 13 items. A decreasing trend for the parameter of failure to maintain set was found, but was not significant ($p = 0.305$). The results of several items are listed in Table 2.

Significant decreases in the completion time in word reading, color reading, word reading in the incongruent condition, and color reading in the incongruent condition were observed in the CH group at month 6 compared with baseline. No significant differences were found in normal controls.

Furthermore, atomoxetine seemed to improve the cognitive functions of children with the inattentive subtype more than those with the other two subtypes according to the WISC-R and Stroop tests. For the other tests, the results did not show any predominant trends in the three groups of subtypes. But because of the small sample size (n = 2, 4, and 6) of the subtypes, it was difficult to do further statistical analyses, and we were unable to draw any definite conclusions. In addition, the medication also benefited the cognitive functions of girls more than those of boys for the WISC-R and Stroop tests. Similarly, because of the small sample size of girls (n = 2), further statistical analyses were not done.

## Discussion

Thyroxine deficiency results in damage to brain development, which may contribute to poor attention and self-inhibition. The extent of the damage may depend on the severity and duration of the hypothyroidism (Klein et al., 1972). But ADHD is sparse in the general population. It is not clear that the occurrence of ADHD in these patients has either a coincidental or causative relationship to CH. Definitely, there are more severe impairments of academic and social functions and quality of life in those with both conditions of CH and ADHD. Taking these impairments into consideration, children with both CH and ADHD should be treated promptly and properly. However, when CH is combined with ADHD the treatment is more challenging. Safety should be the first consideration, ensuring that the treatment does not affect thyroid functions and has good tolerability. Atomoxetine

**Table 1.** Scores of ADHD Symptoms and Thyroid Functions at Baseline and Different Time Points of Post-Treatment

| | Baseline | Week 6 | Week 12 | Month 6 | Statistics |
|---|---|---|---|---|---|
| SNAP-IV (parent) | 33.8±4.9 | 27.3±4.7 | 20.7±3.1 | 16.9±2.3 | F = 131.5, $p < 0.01$ |
| SNAP-IV (teacher) | 34.3±5.5 | 27.8±4.9 | 21±3.1 | 17.2±3.1 | F = 98.7, $p < 0.01$ |
| CGI-S | 5.1±1.2 | 4.3±0.6 | 3.8±0.6 | 3.2±0.8 | F = 11.6, $p < 0.01$ |
| Thyroid function | | | | | |
| Triiodothyronine (Normal range: 0.88–2.44 nmol/L) | 2.3±0.3 | 2.2±0.3 | 2.2±0.2 | 2.2±0.2 | F = 0.34, $p = 0.79$ |
| Thyroxine (Normal range: 62.68–150.8 nmol/L) | 136.9±14.0 | 135.3±12.5 | 135.6±13.8 | 140.0±13.8 | F = 0.13, $p = 0.94$ |
| Thyroid stimulating hormone (Normal range: 0.35–4.94 mIU/L) | 3.4±0.7 | 3.3±0.6 | 3.2±0.7 | 3.3±0.7 | F = 2.58, $p = 0.07$ |

CGI-S, Clinical Global Impression-Severity scale; SNAP-IV, Swanson, Nolan and Pelham (SNAP) Questionnaire.

**Table 2.** Cognitive Functions Between ATX Treatment Group and Controls at Baseline and Month 6

| | ATX group (n = 12) | | | Normal controls (n = 13) | | |
|---|---|---|---|---|---|---|
| Test | Baseline | Month 6 | Statistics | Baseline | Month 6 | Statistics |
| WISC-R | 96.1±8.0 | 100.1±6.9 | t = 3.91, $p$ = 0.002 | 104.1±6.6* | 103.2±6.9* | t=0.306, P=0.765 |
| VIQ | 97.5±6.7 | 99.5±5.3 | t = 1.25, $p$ = 0.239 | 103.2±5.8* | 101.1±5.3 | t=0.856, P=0.409 |
| PIQ | 95.2±9.2 | 100.8±9.3 | t = 3.06, $p$ = 0.011 | 103.3±8.4* | 104.5±9.4* | t=-0.323, P=0.752 |
| Digit Span | 10.5±2.3 | 11.9±1.7 | t = 4.926, $p$ = 0.00 | 12.5±2.6* | 13.5±2.0* | t=-1.848, P=0.089 |
| Forward | 7.7±2.0 | 8.5±1.1 | t = 2.278, $p$ = 0.044 | 9.1±1.8* | 9.7±1.7* | t=-1.76, P=0.104 |
| Backward | 2.8±0.4 | 3.4±1.0 | t = 2.028, $p$ = 0.067 | 3.5±1.2 | 3.8±0.7 | t=-1.298, P=0.219 |
| WCST | | | | | | |
| Perseverative errors | 23.2±4.2 | 21.3±4.5 | t = 4.815, $p$ = 0.001 | 19.9±5.6 | 19.0±5.6* | t=1.760, P=0.104 |
| Conceptual level responses (%) | 44.1±10.4 | 48.0±12.6 | t = 3.829, $p$ = 0.003 | 53.3±11.3* | 58.3±12.9* | t=3.125, P=0.009 |
| Failure to maintain set | 1.1±0.9 | 0.75±0.9 | t = 1.076, $p$ = 0.305 | 1.2±1.0 | 1.1±0.8 | t=0.365, P=0.721 |
| Number of categories completed | 3.1±1.5 | 4.2±0.7 | t = 3.463, $p$ = 0.005 | 3.8±1.4* | 4.2±0.8 | t=1.897, P=0.082 |
| Stroop Test | | | | | | |
| Word (Time in sec) | 24.2±9.1 | 20.4±7.0 | t = 3.515, $p$ = 0.005 | 16.5±2.6* | 16.1±2.7* | t=1.000, P=0.338 |
| Color (Time in sec) | 22.3±6.3 | 20.3±5.3 | t = 5.354, $p$ = 0.00 | 14.7±3.1*† | 14.2±2.5*† | t=1.289, P=0.222 |
| Incongruent condition-word (Time in sec) | 21.8±5.3 | 19.5±4.1 | t = 4.553, $p$ = 0.001 | 15.5±2.5*† | 14.8±2.1*† | t=1.996, P=0.069 |
| Incongruent condition-color (Time in sec) | 29.9±10.7 | 26.8±9.8 | t = 5.636, $p$ = 0.00 | 22.9±4.2* | 21.8±4.1* | t=2.941, P=0.012 |

ATX, atomoxetine; PIQ, performance intelligent quotient; VIQ, verbal intelligent quotient; WCST, Wisconsin Card Sorting Test; WISC-R, Wechsler Intelligence Scale for Chinese Children-revised

*$p$ < 0.05 versus ATX treated group at the baseline; †$p$ < 0.05 versus ATX treated group at month 6 (using t-test)

is a new compound that has been used in treatment for ADHD on the basis of its pharmacologic property of blocking the presynaptic norepinephrine transporter. The efficacy and safety of atomoxetine have been indicated in multiple double-blind, placebo-controlled studies. We treated the patients in the pilot study with atomoxetine. To our knowledge, this is the first trial concerning the efficacy and tolerability of the medication on the cognitive functions in children with CH, diagnosed and treated early, and with ADHD symptoms.

We found that the ADHD symptoms were greatly improved with treatment of atomoxetine. The SNAP-IV and CGI-S scores decreased greatly, which meant the ADHD core symptoms were improved. We also found that this medication was effective on cognitive functions during the 6-month follow-up. The IQs were increased with statistically significant differences according to the WISC-R. The results of cognitive functions, evaluated with the Digit Span, WCST, and Stroop test, which were impaired before treatment, were also showing improvements after atomoxetine administration. These results were consistent with the treatment outcomes of atomoxetine on children with only ADHD symptoms (Vaughan et al., 2009).

We explored but found no significant improvement of cognitive functions and score changes of ADHD symptoms. This was inconsistent with a previous report (Zhang et al., 2011). We speculated the small sample size contributed to it.

In addition, we found that atomoxetine seemed to improve the cognitive functions of children with the inattentive subtype based on the WISC-R and Stroop tests. Similar results revealed that the medication benefited the cognitive functions of girls more than boys for the WISC-R and Stroop tests. In clinical trials of atomoxetine treatment for children with ADHD, there were no findings showing these trends, but the small sample size in the present study did not allow us to do further statistical analyses and we could not draw definite conclusions.

Clinical safety was indicated by means of the child's and parents' reports of adverse events, ECGs, and laboratory tests of thyroid functions, which we did before treatment and at week 6, week 12, and month 6 (Table 1). Three children reported mild adverse events, but none discontinued treatment because of side effects. All the laboratory indicators were normal, showing good tolerability and safety of atomoxetine.

Interestingly, atomoxetine was also effective on one boy in the treatment group who was diagnosed with CH at 18 months. As is well known, thyroxine is crucial for the development of brain, even in utero. The 18-month age was too late for levothyroxine replacement and the damage had already occurred. Fortunately, atomoxetine was effective for improvement of cognitive functions, including IQ (from 78 to 85). In other words, atomoxetine benefited a child who was developmentally delayed, which was consistent with a previous study (Fernandez-Jaen et al., 2010).

This was a pilot trial to explore the treatment strategy for children with both diseases. Further studies should be performed to replicate the results.

### Limitations of this Study

There are several limitations of this study. Firstly, the sample size was too small, which decreased the statistical power. But it was a pilot study, and further larger sample-sized trials should be designed to replicate the results. Secondly, it was not a randomized, placebo-controlled trial. The scale scores rated by observers would be distorted to some extent in the open-labeled pattern. Moreover, we did not include a control group of children who were affected with CH but without ADHD. If there had been this group, the improvement of the atomoxetine-treated group could be examined for the effect of medication and we could exclude the effect of levothyroxine on cognition. Thirdly, the follow-up of 6 months might be relatively short, and longer treatment times would provide more data.

## Conclusion

Those children with CH still have poor attention and self-inhibitory (ADHD symptoms) even with early levothyroxine replacement. Atomoxetine was effective and safe in cases with CH

and ADHD, and produced remarkable improvement on ADHD symptoms as well as cognitive functions within 6 months of follow-up. But the appropriate dosage and other treatment strategies should be further explored. Long-term, randomized, placebo-controlled clinical trials with larger sample sizes are required.

## Acknowledgements

This research did not receive any specific grants from any funding agencies in the public, commercial, or not-for-profit sectors. We thank all the children and parents who participated in our study.

## Statement of Interest

The authors declare no conflict of interest.

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