Atomoxetine in the Treatment of Adults with Subthreshold and/or Late Onset Attention-Deficit Hyperactivity Disorder-Not Otherwise Specified (ADHD-NOS): A Prospective Open-Label 6-Week Study

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The objective of this study was to evaluate the efficacy and tolerability of atomoxetine hydrochloride (ATX) in the treatment of adults with atypical manifestations of attention-deficit hyperactivity disorder (ADHD) (not otherwise specified [NOS]). We hypothesized that treatment with ATX will be safe and efficacious for the treatment of adults with ADHD-NOS. This was a 6-week, open-label, prospective treatment study of ATX monotherapy in 45 adult patients with ADHD-NOS assessed using standardized instruments for diagnosis and a robust oral daily dose of up to 1.2 mg/kg/day or 120 mg/day. Symptom severity was assessed with the adult ADHD Investigator Symptom Report Scale (AISRS) and Clinical Global Impression Scale. Treatment with ATX at an average daily dose of 78.7 ± 27.8 mg was associated with a statistically and clinically significant reduction in ADHD symptoms relative to baseline as assessed through the (AISRS) (-12.1 ± 8.4 ; $P < 0.001$). Using a categorical definition of response (CGI-I much or very much improved), a majority ($N = 29$; 64%) of subjects were rated as improved at study endpoint. Treatment with ATX was relatively well tolerated. These open-label results suggest that ATX may be safe and effective in the treatment of adults meeting criteria for ADHD-NOS and support the need for further controlled clinical trials of ATX in this population.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurobiological disorder associated with high morbidity and disability. Although initially considered a pediatric disorder, it is now estimated that up to 5% of adults across the world suffer from ADHD [1]. Like its pediatric counterpart, ADHD in adults is associated with a wide range of emotional and functional impairments impacting all aspects of the subject's life [2–4]. Although its etiology remains unknown, there is mounting evidence for genetic transmission [5,6] and abnormalities in brain structure and function in affected individuals [7–9].

Despite advances in the recognition of adult ADHD, many patients present with atypical manifestations of the

disorder characterized by later age of onset or insufficient symptoms to qualify for the full diagnosis (ADHD not otherwise specified [NOS]). Faraone et al. [10] recently demonstrated through structured assessments and familial risk analysis that subjects with ADHD and those with late-onset ADHD-NOS had similar patterns of psychiatric comorbidity, functional impairment, and familial transmission. However, because subjects with ADHD-NOS are systematically excluded from clinical trials evaluating treatments for adults with ADHD, they remain therapeutic orphans. There have been only two prior studies, to our knowledge, of adults with ADHD-NOS. Biederman et al. (2006) demonstrated the efficacy and tolerability of OROS methylphenidate in an open-label clinical trial study of late-onset ADHD [3] and Reinhardt et al. also

demonstrated improvement of late-onset ADHD during open-label methylphenidate treatment [11].

Atomoxetine hydrochloride (ATX) is a norepinephrine specific reuptake inhibitor that has received FDA approval as a safe and effective treatment for adults with ADHD at doses of up to 100 mg/day [12]. Atomoxetine may address the disorder by compensating for deficits in noradrenergic tone that are thought to contribute to ADHD [13], and is an important alternative to stimulant treatment due to its low abuse potential [14]. However, because the pivotal studies that led to the FDA approval of atomoxetine for the treatment of adults with ADHD excluded subjects with ADHD-NOS, more information is needed to evaluate the effectiveness and tolerability of ATX in the treatments of adults with ADHD-NOS [15].

The main aim of this study was to evaluate the safety and effectiveness of ATX in the treatment of adults with ADHD-NOS. To this end we conducted an open-label, 6-week pilot study of ATX in adults with DSM-IV ADHD using a similar dosing approach as previously used in the two randomized, double blind 10-week registration trials of ATX in the treatment of adults with a full DSM-IV diagnosis of ADHD. This proof of concept study was conducted in open-label fashion to determine if further, more rigorous, double-blind study of atomoxetine for ADHD-NOS is warranted. We hypothesized that treatment with ATX would be well tolerated and associated with reductions in ADHD symptomatology in adults with ADHD-NOS.

Methods

Subjects

Subjects were outpatient adults with ADHD 19–56 years of age. To be included, subjects had to have a diagnosis of ADHD-NOS, as per DSM-IV criteria, and as manifested in clinical evaluation and confirmed by structured interview. ADHD-NOS was operationalized as: (1) late onset: meeting full current symptom criteria for ADHD, with at least six out of nine current items of either inattention or hyperactivity/impulsivity but onset of symptoms after the age of seven; or (2) subthreshold: having at least five but less than six out of nine current DSM-IV items within the inattention or hyperactivity/impulsivity categories, but meeting the age of onset criteria with symptoms by age 7; or (3) late onset and subthreshold: having at least five but less than six does not meet current symptom criteria but has five current symptoms of either impulsivity-hyperactivity or inattention, and does not meet onset criteria with symptoms by age 7. Subjects needed to have a current Clinical Global Impression of Severity (CGI-S) ADHD score of four (moderately ill) or

higher. Subjects with a past history of depression or anxiety disorder (including OCD) without a current disorder for at least 3 months as ascertained through structured diagnostic interview and clinical exam were allowed to participate. Subjects treated for anxiety disorders and depression who were on a stable medication regimen for at least 3 months, and who had a disorder specific CGI-Severity score ≤ 3 (mildly ill or better), and who have a score on the Hamilton-Depression and Hamilton-Anxiety rating scale below 15 (mild range) were included in the study. Subjects receiving stable doses of benzodiazepines, antihypertensives, or who had been on antidepressants other than a monoamine oxidase inhibitors for at least three months, were eligible for the study.

We excluded potential subjects if they had any organic brain disorders, any metabolic, neurological, hepatic, renal, cardiovascular, hematological, ophthalmic, or endocrine disease, an IQ < 75, any clinically unstable psychiatric conditions (i.e., acute psychosis, acute panic, acute OCD, acute mania, acute suicidality, lifetime history of bipolar disorder, sociopathy, criminality, or abnormal baseline laboratory values), drug or alcohol abuse or dependence within the 6 months preceding the study, or a previous adequate trial of ATX. We also excluded pregnant or nursing females. This study was approved by the Massachusetts General Hospital institutional review board and all subjects completed a written informed consent.

This was an open-label, 6-week study of ATX monotherapy. Treatment was initiated at 0.5 mg/kg/day at the baseline visit and increased to 1.0 mg/kg/day at week 1. Subjects were titrated up to the lesser of 1.2 mg/kg/day or 120 mg/day as tolerated. Divided dosing was allowed when better tolerated.

Assessment

Patients underwent a comprehensive clinical assessment, including a psychiatric evaluation by a board certified psychiatrist, structured diagnostic interview, medical history, vital signs, and laboratory assessments (liver function tests, complete blood count, weight, vital signs, and electrocardiogram). The Structured Clinical Interview for DSM-IV [16] was used and supplemented for childhood disorders by modules (DSM-IV ADHD and conduct disorder) from the Kiddie SADS-E Epidemiologic Version [17].

Overall severity and change in severity of ADHD was assessed with the Clinical Global Impression Scale (CGI) [18]. The CGI includes Global Severity (1 = not ill; 7 = extremely ill) and the Global Improvement (1 = very much improved; 7 = very much worse) scales. The Adult ADHD Investigator System Report Scale (AISRS) [19] has been shown to be sensitive to drug effects in adult

populations [20–23] and was used to assess each of the 18 individual criteria symptoms of ADHD in DSM-IV on a severity grid (0 = not present; 3 = severe; minimum score = 0; maximum score = 54). The Global Assessment of Functioning scale, a global measure of psychosocial functioning, was rated according to guidelines in DSM-IV [24]. Adverse events were elicited by spontaneous reports through open-ended questions at each visit. Weight and vital signs were obtained at each visit.

Statistical Analysis

All analyses were intention to treat with the last observation carried forward (LOCF) for subjects who did not complete the full study schedule. Baseline and endpoint AISRS scores, cardiovascular parameters, weight, and body mass index (BMI) were compared using paired *t*-tests. Statistical significance was determined at α level 0.05.

Results

A total of 45 subjects with ADHD-NOS ($N = 43$ with late onset ADHD (onset after age 7), $N = 1$ with subthreshold ADHD (5/9 current inattentive symptoms), and $N = 1$ with both late onset and subthreshold ADHD) were enrolled and treated with ATX; 33 (73%) completed the trial and dropouts were due to noncompliance ($N = 2$), losses to follow-up ($N = 6$), and adverse effects ($N = 4$). Demographic characteristics of the sample are presented in Table 1. Subjects had a mean age of 39.5 ± 9.6 years, were of predominantly middle class, and 58% were male. The clinical presentation of ADHD is listed in Table 2: subjects had many currently impairing symptoms of ADHD, but reported that symptoms did not onset until early adolescence on average (13.6 years, $SD = 5.5$). Thirty-six percent met lifetime criteria for psychiatric mental health comorbidity other than a substance use disorder and 47% had a past history of substance use disorder (Table 2). In the past month no subjects had a mood disorder, antisocial personality disorder, or a substance use disorder. Three subjects had multiple (≥ 2) anxiety disorders in the past month. Seven subjects were taking concomitant medication at baseline (selective serotonin reuptake inhibitor [SSRI], $N = 3$; benzodiazepine, $N =$

Table 1 Demographic characteristics of 45 adults with ADHD-NOS

	N (%) or mean $\pm$ SD
% Male	26 (58)
Age (years)	39.5 ± 9.6
Hollingshead socioeconomic status	1.9 ± 1.1

Table 2 Clinical characteristics of 45 adults with ADHD-NOS

N (%) or mean ± SD	
ADHD	
Age at onset (years)	13.6 ± 5.5
% Combined subtype	7 (16)
% Inattentive subtype	36 (80)
% Hyperactive/impulsive subtype	2 (4)
Number of current symptoms	10.1 ± 2.6
Number of inattentive symptoms	7.1 ± 1.5
Number of hyperactive/impulsive symptoms	3.0 ± 2.2
CGI severity	
% Moderate	36 (80)
% Marked	9 (20)
	Lifetime
Psychiatric comorbidity	16 (36)
Major depression (severe impairment)	4 (9)
Bipolar disorder	0 (0)
Multiple (≥2) anxiety disorders	9 (20)
Antisocial personality disorder	4 (9)
Conduct disorder	4 (9)
Substance use disorder	21 (47)
Alcohol abuse/dependence	19 (42)
Drug abuse/dependence	10 (22)
Global assessment of functioning	52.2 ± 4.8
	Current (last month)
	3 (7)
	0 (0)
	0 (0)
	3 (7)
	0 (0)
	0 (0)
	0 (0)
	0 (0)
	0 (0)
	59.2 ± 4.0

1; serotonin–norepinephrine reuptake inhibitor [SNRI], $N = 1$; benzodiazepine and SNRI, $N = 1$; nefazodone and SNRI, $N = 1$). One subject receiving SSRI discontinued after week 1. The subject taking SNRI and benzodiazepine discontinued the benzodiazepine after baseline. All other medication treatment was continued throughout the study.

Efficacy

The mean daily dose at week 6 was 78.7 ± 27.8 . As Figure 1A shows, there was a statistically and clinically significant reduction in ADHD symptoms in subjects treated with ATX. There were significant reductions of symptoms of both inattention (-8.0 ± 6.0) and hyperactivity/impulsivity (-4.1 ± 3.7) (Figure 1B). Endpoint AISRS change scores were not statistically significantly different in those with or without a history of psychiatric comorbidity (-11.2 ± 8.2 vs. -12.6 ± 8.5 , $P = 0.61$) or with or without concomitant pharmacotherapy (-9.6 ± 10.0 vs. -12.6 ± 8.1 , $P = 0.39$). Figure 1C shows that there was a greater percent change in ADHD symptom ratings in our study than in two placebo-controlled 10-week studies that used similar dosing strategies that utilized a different ADHD rating scale [15]. Figure 2 shows

Figure 1 AISRS scores.

Figure 2 Clinical ratings of improvement response.

results of various categorical definitions of response (CGI-I ≤ 2 , much or very much improved), 64% (N = 29) of subjects improved at study endpoint. In addition, 69% (N = 31) of subjects had at least a 30% reduction in the

AISRS, 53% (N = 24) had at least a 50% reduction in the AISRS, and 53% (N = 24) had a final AISRS score of 12 or less (remitted). Our a priori definition of response was much or very much improved on the CGI plus a >30%

reduction in symptoms on the AISRS. Using the LOCF analysis, 64% ($N = 29$) of subjects receiving ATX were considered responders.

Adverse Effects

Dry mouth, gastrointestinal distress, insomnia, tiredness/fatigue, headache, and decreased appetite were each reported by over 30% of participants (see Table 3). Although treatment with ATX was not associated with a significant change in weight (-0.8 ± 2.7 kg, $P = 0.06$), there was a small but statistically significant decrease in BMI (-0.3 ± 0.9 kg/m², $P = 0.046$). The average BMI at endpoint was 28.1 ± 7.1 kg/m².

As shown in Table 4, treatment with ATX was associated with small but statistically significant increases in diastolic BP and heart rate, and significant decreases

Table 3 Adverse effects reported in 45 adults with ADHD-NOS treated with Strattera

Adverse effects	N (%)	N persisting ^a (%)
Dry mouth	26 (58)	12 (46)
Gastrointestinal	22 (49)	5 (23)
Insomnia	22 (49)	4 (18)
Tired/fatigued	22 (49)	2 (9)
Headache	17 (38)	6 (35)
Decreased appetite	15 (33)	1 (7)
Warmth/flushing/sweating	13 (29)	4 (31)
Colds/allergies/infections	11 (24)	0
Lightheaded/dizzy	10 (22)	0
Musculoskeletal discomfort	9 (20)	2 (22)
Tension/jitteriness	9 (20)	2 (22)
Mood change	7 (16)	0
Sexual function	7 (16)	3 (43)
Urinary hesitancy	6 (13)	5 (83)
Neurologic	5 (11)	0
Vision/ocular	5 (11)	0
Feeling cold	4 (9)	1 (25)
Injury	4 (9)	0
Muscle twitch/tremor	4 (9)	1 (25)
Impaired concentration	3 (7)	0
Palpitations	3 (7)	2 (67)
Tingling sensation	3 (7)	1 (33)
Vivid dreams	3 (7)	0
Anxiety	2 (4)	0
Bad taste	2 (4)	1 (50)
Chest discomfort	2 (4)	0
Skin changes	2 (4)	0
Increased appetite	1 (2)	1 (100)
Paresthesia	1 (2)	0
Shortness of breath	1 (2)	0
Urinary incontinence	1 (2)	1 (100)

^a Persistence is indicated for adverse events reported at three or more visits by an individual subject. Data from six subjects with less than three visits was excluded.

Table 4 Measures of cardiac functioning (mean $\pm$ SD)

	Baseline	Endpoint	Test statistic	P-value
Systolic BP	122.8 $\pm$ 15.0	122.1 $\pm$ 13.5	$t_{(44)} = 0.33$	0.74
Diastolic BP	72.3 $\pm$ 9.8	75.6 $\pm$ 9.0	$t_{(44)} = -3.24$	0.002
Heart rate	74.2 $\pm$ 11.0	83.3 $\pm$ 13.1	$t_{(44)} = -5.66$	<0.001
PR interval	155.7 $\pm$ 18.2	151.0 $\pm$ 17.9	$t_{(43)} = 2.27$	0.03
QRS interval	90.6 $\pm$ 12.0	89.8 $\pm$ 11.7	$t_{(44)} = 1.26$	0.21
QT interval	388.8 $\pm$ 28.4	376.0 $\pm$ 28.2	$t_{(44)} = 4.11$	<0.001
QTC interval	409.7 $\pm$ 14.7	411.9 $\pm$ 15.2	$t_{(44)} = -1.25$	0.22

in PR and QT interval. Further examination of cardiovascular parameters revealed 13 subjects (29%) with a heart rate ≥ 100 BPM (maximum value = 123 BPM) at some point in the study. Only four subjects (9%) had persistent (at least two consecutive readings) heart rate ≥ 100 BPM. Their baseline heart rates were 80, 80, 85, and 96. Eight subjects (18%) had a systolic blood pressure of ≥ 140 mmHg at some point in the study (maximum value = 164 mmHg). Only two subjects (4%) had persistent systolic blood pressure of ≥ 140 mmHg, and both of these subjects had systolic blood pressure > 135 mmHg at baseline. Eight subjects (18%) had a diastolic blood pressure of ≥ 90 mmHg (maximum value = 100 mmHg). Only four subjects (9%) had persistent diastolic blood pressure of ≥ 90 mmHg, and two of these subjects had diastolic blood pressure ≥ 85 mmHg at baseline. No subject had a QTc interval of ≥ 460 ms.

Four subjects were dropped due to adverse effects. The following adverse effects were their reasons for discontinuation: (1) dry mouth, reduced sex drive, and fatigue; (2) depressed mood; (3) tension; and (4) moodiness and urinary retention.

Discussion

This 6 week, open-label trial of ATX in adults with ADHD-NOS documented that treatment with ATX at an oral daily dose of up to 1.2 mg/kg/day or 120 mg/day (whichever was less) was associated with a clinically and statically significant response. The overall response rate for ADHD symptoms was of similar magnitude as that observed in two large, parallel design, placebo controlled, randomized clinical trials of ATX [15] that demonstrated the efficacy and tolerability of ATX in adults with a full DSM-IV diagnosis of ADHD. To our knowledge, this is the first clinical trial of atomoxetine for the treatment of adults with ADHD-NOS.

As in the double-blind registration studies of ATX treatment for DSM-IV ADHD, treatment with ATX was generally well tolerated by adults with ADHD-NOS [15]. There were no serious adverse effects. The most

commonly reported adverse effects, each reported by over 30% of participants, were dry mouth, gastrointestinal distress, insomnia, headache, decreased appetite, and tiredness/fatigue. It is notable that a higher proportion of subjects experienced some of these side effects than was reported in the registration trials for Atomoxetine [15]. The higher rate of adverse events in our study might be explained by the following differences from the registration trials: no placebo, no placebo lead-in, weekly dose increase rather than every 2 weeks, and initial daily dosing rather than divided. ATX exposure was associated with a small but significant decrease in BMI (-0.3 ± 0.9 kg/m²) over the course of the 6-week trial. Treatment with ATX was also associated with mild but significant elevations in diastolic blood pressure and heart rate. Although statistically significant cardiovascular findings were small in the group data, a minority of ATX-treated subjects had persistent tachycardia (>100 bpm, 9%), high systolic blood pressure (>140 mmHg, 4%), or persistently high diastolic blood pressure (>90 mmHg, 9%). It is notable that of the five subjects who accounted for these persistent hypertensive readings, all but one had baseline blood pressures falling in the prehypertensive category (120–139/80–89). Thus, adults with ADHD should be monitored for changes in weight, heart rate, and blood pressure during ATX treatment, particularly those who are prehypertensive or those who are underweight.

Our findings must be seen in light of methodological limitations. Because this was a small, open-label study, our results should be viewed with caution until confirmed in more rigorous randomized clinical trials. Although the tolerability results of this study are reassuring, a much larger sample size or a systematic assessment of adverse effects is needed to fully assess the occurrence of rare adverse events. Because of the relatively short exposure to medication, more work is needed to assess whether initial improvement will be persistent overtime.

Despite these considerations, this open-label clinical trial of ATX in the treatment of adults with ADHD-NOS showed that treatment with ATX in doses of up to 1.2 mg/kg/day was associated with robust statistical and clinical improvement of ADHD symptoms and was well tolerated. These results support the need for randomized clinical trials evaluating the short- and long-term efficacy and safety of ATX in the treatment of adults with atypical manifestations of ADHD.

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In the past 2 years, Dr. Hammerness has received research funds or participated in CME activities/professional talks supported by the following pharmaceutical companies: Abbott, Eli Lilly, Forest, McNeil, Shire. Dr. Hammerness has also received research funds from Elminda Ltd and has participated in speaker training and served on the advisory board for Shire. Dr. Hammerness has participated, as an investigator, in research studies funded by the following pharmaceutical companies: Abbott, Bristol Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, McNeil, Merck, New River, Organon, Pfizer, Shire, Takeda. Dr. Hammerness has also received honoraria from Reed Medical Education (logistics collaborator for the MGH Psychiatry Academy). Commercial entities supporting the MGH Psychiatry Academy are listed on the Academy's website, <http://www.mghcme.org>.

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