

Clinical Course of Adult ADHD Patients Treated with Atomoxetine

Stephanie R. Wilson, PharmD, Staff Pharmacist, Wal-Mart, Leeds, AL
(Dr. Wilson was a PharmD candidate at McWhorter School of Pharmacy, Samford University, Birmingham, AL, when this paper was submitted)

Rachel E. Fargason, MD, Associate Professor, University of Alabama at Birmingham School of Medicine, Birmingham, AL

Marshall E. Cates, PharmD, BCPP, FASHP, Professor of Pharmacy Practice, Samford University, Birmingham, AL (Dr. Cates was also the Sponsoring Faculty for this student paper)

Pamela J. Sims, PharmD, PhD, Professor and Chair, Department of Pharmaceutical, Social, and Administrative Sciences, Samford University, Birmingham, AL

Angela A. Boggs, PharmD, Clinical Pharmacist, University of Maryland-Baltimore, MD

Abstract

Introduction: Atomoxetine was the first FDA approved non-stimulant for the treatment of adult ADHD. Very little is known about the clinical course of adult ADHD patients treated with atomoxetine, especially for cases involving comorbid psychiatric disorders.

Methods: The design was a retrospective study of adult ADHD patients treated with atomoxetine at a specialized clinic. The primary efficacy measure was the Clinical Global Impressions-Improvement scale.

Results: Thirty-seven patients were enrolled into the study, most of whom were also diagnosed with depression (24/37). Approximately one-half (18/37) of patients were rated as responders to therapy based on CGI-I score of 1 or 2. Those patients with comorbid psychiatric disorders had a higher response rate than did those patients without comorbid psychiatric disorders (56% vs. 33%). Most patients were switched to atomoxetine from previous therapies, but those cases in which atomoxetine was added to existing drug therapy showed a higher response rate. Therapy was discontinued in 21 cases, usually owing to adverse effects (11/37). Men were more than twice as likely as women to discontinue therapy due to adverse effects.

Conclusions: Atomoxetine therapy was effective for adult ADHD patients, especially those with comorbid depression \pm anxiety. Atomoxetine therapy was particularly effective as an adjunctive agent in cases of partial response to previous therapy. The discontinuation rate due to adverse effects was comparatively high, especially for male patients.

Key words: atomoxetine, attention-deficit/hyperactivity disorder, adult ADHD

Introduction

Attention deficit/hyperactivity disorder (ADHD) is typically first evident in childhood, noted by excessive motor activity, difficulty in sustaining attention, and impulsiveness.[1-4] Historically, clinicians believed that ADHD was a condition that would be “outgrown” in puberty or adulthood, but there is now evidence that a significant number of cases will have symptoms that persist into adulthood.[1,5] Adult ADHD has been associated with higher levels of school failure, poor work history, and low self-esteem.[5] Adult patients seem to have a more difficult time dealing with the stress of everyday life, especially for those trying to balance work with household management and family planning. Furthermore, adult ADHD is frequently complicated by comorbid mood disorders and substance abuse.[2-3]

While many modalities may be utilized in treatment for adult ADHD, including support groups, coping strategies, skills training, and coaching to handle difficult situations, pharmacotherapy remains first line in the effective management of the disorder.[2-5] Stimulant therapy has been the treatment of choice, showing the greatest amount of efficacy compared to tricyclic antidepressants and bupropion, which have also been used in treatment of ADHD treatment.[2-4] Methylphenidate and mixed amphetamine salts are the agents of choice; however, caution must be used in patients with substance abuse potential. The longer-acting preparations are better tolerated and have lower abuse potential.[3-4] Adverse effects from stimulants are generally mild and may include decreased appetite, insomnia, headache or nervousness.[4] Tricyclic antidepressants have shown moderate improvement for adult patients with ADHD, however the side effect profile tends to be more severe. Constipation, dry mouth, postural hypotension, and tachycardia may be experienced.[3-4]

The newest treatment option, and the first FDA approved non-stimulant indicated for the treatment of adult ADHD, is atomoxetine (Strattera®).[6] Atomoxetine is a selective norepinephrine reuptake inhibitor with mild antidepressant activity.[6-7] It does not affect extracellular dopamine levels in the striatum or nucleus accumbens, a brain region associated with psychostimulation and rewarding properties of drugs of abuse.[6] Atomoxetine is considered a valuable treatment option, especially in patients with substance abuse potential or those not wishing to take a controlled substance.[8]

Two nearly identical, randomized, controlled clinical trials were conducted in adults to establish safety and efficacy of atomoxetine in ADHD.[9] In the first trial, 280 adults between 18 and 67 were included to take either atomoxetine (n=141) or placebo (n=139) twice daily, in the morning and early evening for 10 weeks. The second trial included 256 adults between 18 and 76 to take either atomoxetine or placebo twice daily, in the morning and early evening for 10 weeks.[9] The total daily dose (TDD) was 60mg at the initiation of the trial and was titrated up to 120mg TDD at 4 weeks, if needed, based on patient response. Patients were required to have verifiable symptoms of ADHD in childhood, persisting into adulthood. Patients were excluded if they had concurrent anxiety or depression, past or current psychotic or bipolar disorders, serious medical illness, or alcohol or substance abuse. The primary endpoint, reduction in total ADHD symptoms, was measured by the Conners' Adult Attention Rating Scale (CAARS), which is completed by the patient and/or an observer such as a spouse, parent, or friend. It uses a scale of 0–4 (not at all, just a little, pretty much, very much). *The Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) ADHD criteria can be extracted from CAARS, which validates its usefulness in these trials. In both studies, atomoxetine demonstrated statistically significantly improved CAARS scores versus placebo. No significant differences were seen based on population subsets of gender or age.[6,8] In both trials, atomoxetine was well tolerated, as adverse effects were generally mild and transient. Only 9 of the 270 patients treated with atomoxetine withdrew from the trials due to treatment-related adverse effects: insomnia (n=3), chest pain (n=2), palpitations (n=2), and urinary retention (n=2).[8]

Atomoxetine was introduced to the market in December 2002, holding what many clinicians believed was great promise for a new type of treatment for adult ADHD. However, there have been no trials following the natural clinical course of patients who were treated with atomoxetine as either monotherapy or adjunctive therapy to determine its long-term safety and efficacy. Furthermore, trials typically exclude patients with comorbid psychiatric disorders. [6] The majority of adult ADHD patients in clinical practice

suffer from comorbid psychiatric disorders. The purpose of this study was to determine the efficacy and tolerability of atomoxetine therapy for adult ADHD in the usual clinical setting.

Methods

This study was approved by the Institutional Review Boards of Samford University and University of Alabama at Birmingham (UAB). A waiver of informed consent was obtained prior to the study. The study was conducted at the adult ADHD clinic of UAB. A computerized search of medical records was conducted to identify the names of all patients who had the diagnosis of attention deficit disorder with or without hyperactivity electronically coded on a visit in the adult ADHD clinic at the University of Alabama at Birmingham. All charts were reviewed to select patients meeting the following inclusion criteria: ages 19-65; diagnosed with ADHD of any subtype; prescribed atomoxetine as monotherapy or adjunctive therapy since December 2002; had at least an initial assessment and one follow-up session with documented adverse effect and efficacy data.

Data collection included demographic information, comorbid disease states, concurrent psychotropic medications, and clinical course for treatment of ADHD. The progress notes were evaluated for efficacy using the Clinical Global Impression for Improvement scale (CGI-I) at the most recent follow-up visit as compared to the baseline visit when atomoxetine therapy was initiated.[10] Safety was evaluated based on adverse effects recorded by the clinician at each follow-up visit. Adverse effects were categorized as those causing termination of therapy and those not causing termination of therapy.

The CGI-I is a widely used tool to determine outcome measures in treatment studies of psychiatric disorders. The investigator determined CGI-I rating based on the data collected from the last recorded follow-up visit. The CGI-I is a scale from 1-7 that quantifies a clinician-rated global impression of improvement in the patient's psychiatric illness based on the following modifiers: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, or 7 = very much worse. Ratings were performed by 2 of the authors (Wilson & Fargason) based on assessments of treatment response as recorded in progress notes (originally written by Fargason). As determined by the investigators prior to data collection, patients with a CGI-I rating of 1 or 2 were considered responders.[10]

Results

A total of 224 patient charts were reviewed for inclusion in the study, with a total of 37 meeting inclusion criteria. All excluded subjects either did not have a diagnosis of ADHD or had never been treated with atomoxetine. The average age of patients was 42.4 ± 12.3 years. Twenty-five patients had comorbid psychiatric disorders, and over 75% (28/37) were receiving other psychotropic medications. Other demographic information is presented in Table 1.

Nearly one-half (18/37) of patients responded to atomoxetine therapy. Only 5.4% (2/37) of patients had worsening symptoms upon treatment with atomoxetine. The remaining 45.9% of patients were either only minimally improved or had no change in symptoms.

Response rates across age groups were as follows: 19-25: 75.0% (3/4); 26-35: 33.3% (2/6); 36-45: 25.0% (2/8); 46-55: 64.3% (9/14); and >55: 40.0% (2/5). Males responded at a rate of 50.0% (12/24) and females responded at a rate of 46.2% (6/13).

Of the 25 patients with comorbid psychiatric disease states, 14 (56.0%) were responders. Of the 12 patients without comorbid psychiatric disease states, only 4 (33.3%) were responders. Patients with a diagnosis of depression had a response rate of 60.0% (9/15). Patients with depression and anxiety had a response rate of 57.1% (4/7).

Table 1. Demographic variables (n=37)

Variable	Number(%)
Gender	
Male	24 (64.8)
Female	13 (35.3)
Age	
19-25	4 (10.8)
26-35	6 (16.2)
36-45	8 (21.6)
46-55	14 (37.9)
>55	5 (13.5)
Race	
White	37 (100)
Other	0 (0)
Comorbid psychiatric disorders	
Depression	15 (40.5)
Depression + Anxiety	7 (18.9)
Depression + Other	2 (5.4)
Other	1 (2.7)
Other psychotropic agents	28 (75.7)

In approximately one-half of the cases, atomoxetine therapy was initiated via switch from another medication (Table 2). For about one-third of cases, atomoxetine was initiated as monotherapy. A very high response rate (71.4%) was seen in the minority of patients (n=7) who had atomoxetine added to their existing medication for treatment of ADHD.

Table 2. Categories of atomoxetine initiation

Initiation of therapy	Number (%)	Responders: CGI-I of 1 or 2(%)
Initiated as monotherapy	12 (32.4)	4 (33.3)
Switched to atomoxetine	18 (48.6)	9 (50.0)
Atomoxetine added to existing regimen	7 (18.9)	5 (71.4)
Total	37 (100.0)	18 (48.6)

Endpoints of therapy are delineated in Table 3. Sixteen patients were receiving atomoxetine therapy at the time of data collection, including 5 who had another medication added to atomoxetine therapy due to partial response. Atomoxetine therapy was discontinued in more than one-half of cases, usually due to adverse effects.

Table 3. Endpoints of atomoxetine therapy

Endpoint of therapy	Number(%)
Continued atomoxetine	11 (29.7)
Received supplemental therapy due to partial response	5 (13.5)
Atomoxetine therapy discontinued	
Adverse effects	11 (29.7)
Inefficacy	8 (21.6)
Other	2 (5.4)

Male patients discontinued therapy due to adverse effects at a higher rate than did female patients (Table 4). Sexual dysfunction was the most common adverse effect leading to therapy discontinuation. One patient experienced a hypertensive response, which was considered a severe adverse effect. All adverse effects mentioned in the progress notes were included, but the causal effect of atomoxetine is uncertain.

Adverse effects reported that did not result in termination of therapy are shown in Table 5. Fatigue and irritability were the most common adverse effects. Females were more likely to report fatigue, whereas males were more likely to report irritability.

Discussion

Approximately one-half of adult ADHD patients responded to treatment with atomoxetine based on the categorical endpoint of CGI-I of 1 or 2. Not surprisingly given the mild antidepressant effects of atomoxetine, subjects with a concurrent diagnosis of depression responded at a higher rate than those patients lacking this comorbidity. While some of these patients were also being treated with antidepressants, the antidepressant dosages remained the same during the 2-month period of atomoxetine initiation. Of all patients with comorbid psychiatric disease states, 56% were responders. According to a recent treatment guideline[11], atomoxetine can be used for patients with mood, anxiety, or substance use disorders.

Table 4. Adverse effects resulting in termination of therapy

Adverse effect	Male (n=24)	Female (n=13)
Sexual dysfunction	3	1
Sedation	2	0
Ringing in ears	1	0
Insomnia	0	1
Constipation	2	0
Nausea	1	0
Flat affect	1	0
Hypertension	1	0
Facial tics	1	0
Word formation	1	0
Total (%) *	9 (37.5)	2 (15.4)

* Some patients experienced more than one adverse effect

Table 5. Adverse effects not resulting in termination of therapy

Adverse effect	Male	Female	Total %
GI (bloating, heartburn, gas, diarrhea)	0	1	2.7
Fatigue	2	7	24.3
Sedation	0	1	2.7
Headache	0	2	5.4
Decreased appetite	1	0	2.7
Nausea	0	2	5.4
Dizziness	0	2	5.4
Dry mouth	1	2	8.1
Irritability	4	0	10.8
Insomnia	1	0	2.7
Urinary hesitancy	3	0	8.1
Constipation	1	0	2.7
Sexual dysfunction	1	1	5.4
Word finding difficulties	1	0	2.7

The efficacy data are promising considering that many adult patients are diagnosed with ADHD while being treated for other psychiatric disorders. Another intriguing finding was that over 70% of patients who were prescribed atomoxetine in addition to an existing regimen for ADHD were responders to therapy. Thus, atomoxetine may be particularly effective as an adjunctive agent in the treatment of ADHD.

As anticipated based on the aforementioned phase III trials, atomoxetine caused mainly mild adverse effects, as only one adverse effect was considered severe by the investigators. However, the percentage of our patients who had therapy terminated due to adverse effects--almost 30%--was greater than expected. This could possibly be due to differences between the experimental procedures of phase III trials versus usual clinical practice reflected in the present trial. Interestingly, the percentage of males terminating therapy due to adverse effects was considerably greater than that of females (37.5% versus 15.4%, respectively). The most common adverse effect resulting in termination of therapy was sexual dysfunction. In the phase III trials, no subjects discontinued therapy due to sexual dysfunction, although the adverse event was reported in 12% of subjects. There were also significant differences between genders in the rate of occurrence of certain adverse effects. Fatigue was reported in 7 (53.8%) females vs. 2 (8.3%) males. Urinary hesitancy was reported by 3 (12.5%) males vs. 0 (0.0%) females. Finally, 4 (16.6%) males vs. 0 (0.0%) females reported irritability as a result of atomoxetine therapy. While the cause is unknown, these results introduce the possibility of different adverse effect profiles for patients based on gender.

Limitations

Obvious limitations of the study include its retrospective design and small sample size; however, it is difficult to find a large sample size in a clinic specifically dedicated to adult ADHD. Since response to therapy was determined with a global measure of improvement (i.e., CGI), it is impossible to demarcate improvement of primary symptoms of ADHD versus symptoms of comorbidities.

Adverse effects may have been underestimated due to the retrospective design of the trial (i.e., the patients may have experienced adverse effects that were not recorded in the progress notes). Furthermore, investigators were unable to determine the absolute causation of adverse effects due to the number of variables, such as self-medication with herbals or OTC drugs or concurrent prescription medication. Any adverse effect the patient reported was listed as a possible result of atomoxetine. Reported adverse effects did occur in temporal relationship with initiation of atomoxetine therapy while other medications were held constant.

We were unable to assess compliance, as this data was not always recorded in the charts. Also, patients were able to terminate therapy at any time, with or without the presence of a valid reason for cessation. These factors negatively effect results as they may skew data that otherwise might have appeared more positive. Generalizability of findings is a concern because the study was conducted at a single clinic. Also, all of the subjects were Caucasian.

Conclusions

Despite the limitations of this study, atomoxetine should be considered a valuable treatment option for adult patients with ADHD, especially those with concurrent depression and anxiety symptoms. The majority of patients showed at least minimal improvement with only mild adverse effects, as was anticipated based on previous data from other studies. However, the discontinuation rate due to adverse effects was relatively high, especially for male patients. Further controlled clinical trials with more diverse populations are needed to further characterize the role of atomoxetine therapy in the adult ADHD population.

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