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ADALIMUMAB (HUMIRA™)

NOVEL HUMAN Monoclonal Antibody for THE TREATMENT OF Rheumatoid Arthritis

Anzeela Schentrup, Pharm.D. Candidate

Rheumatoid Arthritis (RA) is a debilitating inflammatory disease that affects about 2.1 million Americans, or 1% of the US adult population. Women are affected 2-3 times more often than men. Although the disease often begins in middle age and occurs with increased frequency in the elderly, children and young adults can also develop RA.[1] The total (direct and indirect) annual cost of RA in the US is approximately $65 billion.[2]

Common symptoms of RA include tender and swollen joints, fatigue, malaise and, occasionally, fever. Over time, the disease leads to joint destruction and loss of function. Other uncommon complications include cardiac, pulmonary and other extra-articular inflammatory consequences. The etiology of rheumatoid arthritis is unknown. Evidence suggests that the disease is a result of an autoimmune process, with certain modulators of inflammation such as tumor necrosis factor (TNF)-a and interleukin 1 playing a significant role. According to the 2002 practice guidelines for the management of rheumatoid arthritis, the goals of treatment are to control joint damage, prevent loss of function, and to decrease pain.

Current treatment strategies for RA include non-steroidal anti-inflammatory drugs (NSAIDs), steroids, and disease-modifying anti-rheumatic drugs (DMARDs). NSAIDs and steroids are useful to treat pain and inflammation associated with RA, but they do not alter the course of the disease nor prevent joint destruction. On the other hand, DMARDs have become the standard of care for RA because they have the potential to reduce or prevent joint damage, preserve joint function and integrity, reduce health-care costs, and maintain patients' economic productivity.

Adalimumab (Humira™) is manufactured by Abbott Laboratories and was approved by the FDA on December 31, 2002 to reduce signs and symptoms and inhibit the progression of structural damage in adult patients with moderately to severely active RA that have had an inadequate response to one or more DMARDs.[3] This article will focus on the pharmacology, pharmacokinetics, toxicity, safety, and clinical applications of adalimumab.

Pharmacology and Pharmacokinetics

Adalimumab is a recombinant human IgG_1 monoclonal antibody specific for human TNF. It is the first product consisting entirely of human peptide sequences and joins etanercept and infliximab in the arsenal of DMARDs available to RA patients. Etanercept is a recombinant TNF receptor:Fc dimeric fusion protein, while infliximab is a chimeric human and murine monoclonal TNF-a antibody. Adalimumab binds specifically to TNF-a and blocks its interaction with the p55 and p75 cell surface receptors. In vitro, adalimumab causes lysis of surface TNF-expressing cells when complement is present. Elevated levels of TNF are found in the synovial fluid of RA patients and are thought to play an important and perhaps dominant role in the development of rheumatoid synovitis and ultimately joint destruction. After treatment with adalimumab, there is a rapid decrease in acute phase reactants such as C-reactive protein and erythrocyte sedimentation rate. A decrease in serum levels of matrix metalloproteinases, which are thought to be responsible for tissue remodeling and

Table 1. Percent of patients with ACR20, ACR50 and ACR70 responses at week 24[4]

Response Criteria	Placebo (N=62)	ADA 20mg qow (N=69)	ADA 40mg qow (N=67)	ADA 80mg qow (N=73)
ACR20*	9 (14.5)	33 (47.8); $p<0.001$	45 (67.2); $p<0.001$	48 (65.8); $p<0.001$
ACR50†	5 (8.1)	22 (31.9); $p=0.003$	37 (55.2); $p<0.001$	31 (42.5); $p<0.001$
ACR70†	3 (4.8)	7 (10.1); *p*-value NS	18 (26.9); $p<0.001$	14 (19.2); $p<0.001$

ADA=adalimumab, N=number of patients, qow=every other week, NS=not significant.
*Adalimumab vs. placebo by Dunnett's test ($p=0.05$). †Adalimumab vs. placebo by unadjusted t-test ($p=0.05$).

for cartilage destruction, was also observed.

Adalimumab is administered as a subcutaneous injection. The C_{max} and T_{max} are 4.7±1.6 ug/mL and 131±56 h, respectively. Adalimumab's bioavailability is 64% and it follows linear pharmacokinetics with a $t_{1/2}$ of approximately 2 weeks. Synovial fluid concentrations ranged from 31-96% of serum levels in five patients. No gender related differences were apparent and no data are available in hepatic/renal impairment. Methotrexate (MTX) reduced apparent clearance by 29% and 44% after single dosing and multiple dosing, respectively.

Clinical Trials

Adalimumab's safety and efficacy was evaluated in 4 randomized, double-blind, placebo-controlled studies. Study I (ARMADA) evaluated 271 patients with active RA who had failed therapy with at least one but no more than four DMARDs and had an inadequate response with MTX. Doses of 20, 40, or 80 mg were administered subcutaneously every other week for 24 weeks. The primary efficacy endpoint was a 20% improvement in the American College of Rheumatology (ACR20) rating criteria. ACR20 response criteria included evaluation of the number of tender and swollen joints, global assessment score by physician and patient, level of pain on a visual analog scale, disability index based on the Health Assessment Questionnaire, and concentration of C-reactive protein. Secondary endpoints included ACR50 and ACR70 ratings. Results are given in Table 1.[4]

Study II evaluated 544 patients who had failed therapy with at least one DMARD. Subjects received placebo, adalimumab 20 mg, or 40 mg every other week or weekly for 26 weeks. Study III evaluated 619 patients who had an inadequate response to MTX. Patients were randomized to receive placebo, adalimumab 40 mg every other week with placebo injections on alternate weeks, or adalimumab 20 mg every week for up to 52 weeks. Primary endpoints were ACR20, ACR50 and ACR70 response rates. This study also evaluated inhibition of disease progression at 52 weeks as detected by radiography. Table 2 summarizes the results from studies II and III.[5] Results from Study III regarding radiographically detected changes between the MTX and adalimumab-MTX combination treatment groups are given in Table 3.[5]

Study IV assessed the safety of adalimumab administration in 636 patients who were either DMARD-naive or were permitted to remain on previous therapy that was stable for a minimum of 28 days. Patients received adalimumab 40 mg or placebo every other week for 24 weeks. Fifty-three patients treated with adalimumab 40 mg every other week plus standard of care had an ACR20 response at week 24, compared to only 35 that received placebo plus standard of care ($p<0.001$). No unique adverse reactions related to the combination of adalimumab with other DMARDS were observed.

All four clinical trials show that adalimumab has the ability to ameliorate the symptoms of RA in active patients. Preliminary findings also show that it intervenes in the progression of the disease, which is similar to that found for both etanercept and infliximab.[5] There are no current head-to-head trials comparing the various biologic DMARDs.

Adverse Effects

Infection is a particular concern in patients treated with monoclonal antibodies. In clinical trials, the rate of infection was 1 per patient/year in adalimumab-treated patients and 0.9 per patient/year in placebo-treated patients. Infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. The

Table 2. Percent of adalimumab-treated patients achieving ACR20, ACR50, and ACR70 responses[5]

Response	Study II Monotherapy (26 wks)			Study III MTX Combination (24 and 52 wks)	
	PBO (N=110)	ADA 40mg qod (N=113)	ADA 40mg qwk (N=103)	PBO/MTX (N=200)	ADA/MTX 40mg qowk (N=207)
ACR20					
Month 6	19%	46%*	53%*	30%*	63%*
Month 12	NA	NA	NA	24%*	59%*
ACR 50					
Month 6	8%	22%*	35%*	10%*	39%*
Month 12	NA	NA	NA	10%*	42%*
ACR70					
Month 6	2%	12%*	18%*	3%*	21%*
Month 12	NA	NA	NA	5%*	23%*

MTX=methotrexate, PBO=placebo, ADA=adalimumab, qod=every other day, qwk=every week, qowk=every other week, N=number patients, NA=not applicable
*p=0.01. All treatment groups in studies II and III showed significant improvements in response criteria ACR20, ACR50, and ACR70.

incidence of serious infections, including pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis was 0.04 per patient/year in adalimumab-treated patients and 0.02 per patient/year in placebo-treated patients. Thirteen cases of tuberculosis and 6 cases of invasive opportunistic infections caused by histoplasma, aspergillus, and nocardia were reported in trials. Therefore, concomitant immunosuppressive therapy increases the risk of infections such as tuberculosis and invasive fungal infections. Treatment with adalimumab should not be initiated in patients with active infections including chronic or localized infections. Careful monitoring is required in treating a patient who develops infections while being treated with TNF antagonists. Patients who reside in areas where histoplasmosis or tuberculosis are endemic are at particular risk. Prior vaccination is a consideration before initiation of therapy.

Among the 2,468 RA patients treated in the four clinical trials, 48 malignancies of various types were observed. In particular, 10 patients developed lymphoma. It is not clear whether this reflects a higher incidence among RA patients or an effect of treatment, however a increase of up to several fold has been reported in the RA patient population. The development of autoantibodies was monitored during clinical trials with an incidence of 12% and 7% in adalimumab– and placebo-treated patients respectively. One patient of 2,334 in clinical trials developed a new-onset lupus-like syndrome that resolved with discontinuation of therapy with no complications. The impact of long-term treatment with adalimumab on the development of autoimmune diseases is unknown. Based on enzyme-linked immunoabsorbent assay (ELISA), approximately 5% (58 of 1,062) of adult rheumatoid arthritis patients in studies I, II, and III developed low-titer autoantibodies to adalimumab that were neutralizing *in vitro*. Combined therapy with MTX showed a 1% incidence of autoantibody development compared to 12% in patients receiving monotherapy. The long-term immunogenicity of adalimumab is unknown.

In clinical trials, the most common adverse reaction from adalimumab was injection site reactions, with an incidence of 20% compared to only 14% in placebo-treated patients. Injection site reactions included erythema, itching, hemorrhage, pain and swelling. Seven percent of adalimumab-treated patients discontinued treatment due to adverse reactions compared to only 4% of placebo-treated patients. The most common adverse reactions that lead to discontinuation were clinical flare reaction (0.7%), rash (0.3%), and pneumonia (0.3%).

Dosage and Administration

Adalimumab is supplied as a preservative-free pre-filled syringe that must be stored under refrigeration. It is administered as a 40 mg subcutaneous injection every other week. Other pharmacological therapies for RA, including NSAIDS, glucocorticoids, and other DMARDs may be continued

Table 3. Mean radiographic changes over 12 months found in Study III[5]

Radiographic Changes	PBO/MTX	ADA/MTX 40mg qow	PBO/MTX-ADA/MTX (95% CI)	*p*-value*
Total Sharp score[5]	2.7	0.1	2.6 (1.4, 3.8)	<0.001
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	<0.001
Joint Space Narrowing score	1.0	0.1	0.9 (0.3, 1.4)	0.002

PBO=placebo, MTX=methotrexate, ADA=adalimumab, qow=every other week, CI=confidence interval,
*Based on rank analysis. Significant improvement in radiographically-detected changes at 1 year of treatment was detected in each criteria chosen.

during treatment. According to study data, in patients not taking concomitant MTX, weekly dosing may be indicated. Injection of adalimumab initially should be supervised. However, self-administration after proper training is appropriate making adalimumab a more convenient alternative than infliximab which is given as a continuous infusion.[5]

Cost

A one-month supply of Humira™ costs approximately $1,200, which is a box with 2 injections. In addition, there are initial administration costs when injections are administered by a health professional and these may vary. Initial tuberculin skin test for latent tuberculosis infection must be conducted prior to initiation and treated if such infection is discovered. Monitoring parameters include antinuclear antibody development due to the development of positive ANA titers in adalimumab treated patients in clinical trials. Since information about the long-term risk of developing lupus-like syndrome is unknown, ANA titers should be monitored at baseline, periodically throughout therapy and with the development of symptoms of new-onset lupus syndrome (manifested by abdominal pain, fever, chills, arthralgia or arthritis, myalgia, pericarditis, pleuritis, and/or skin rash).[7]

Summary

Adalimumab is a new fully human monoclonal antibody available for the treatment of RA, either alone or in combination with other DMARDs. It appears to be as effective as other available biological agents, but head-to-head trials are not available. It offers patients the convenience of every other week administration, which is less often than other currently available biological treatments. In general, it represents a flexible treatment for RA with the promise of true disease modifying ability as evaluated by radiographic evidence.

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ATOMOXETINE (STRATTERA™)

THE FIRST NON-STIMULANT FOR THE TREATMENT OF ADHD

Eric Peters, Pharm.D. Candidate

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric disorder that is characterized by difficulties maintaining attention and problems with impulse control. ADHD has been linked to poor academic performance and impaired social functioning.[1] The American Psychiatric Association estimates that ADHD affects an estimated 3-7% of school aged children,[2] although other sources suggest that the prevalence of ADHD in children may be as high as 10%.[3] Often, the symptoms of ADHD gradually become less problematic as children grow older. In some individuals, the disorder may persist into adulthood resulting in significant morbidity, decreased productivity, and other psychosocial problems.[4]

Until recently, the only pharmacological agents with an FDA approved indication to treat ADHD in children and adults were the stimulant salts methylphenidate and amphetamine. These psychostimulants have demonstrated efficacy, and are considered standard treatment in ADHD. However, adverse effects such as insomnia, anorexia, and irritability have left many patients, parents, and clinicians dissatisfied with these agents. In addition, the psychostimulants are controlled substances, which have a high potential for abuse and diversion. Other non-stimulants including desipramine and bupropion have demonstrated a reduction in ADHD symptoms,[5] but to date have not been approved for children and adults with ADHD.

Atomoxetine (Strattera™) is the first non-stimulant agent approved for ADHD. The FDA granted atomoxetine approval for the treatment of ADHD on December 3, 2002. Eli Lilly and Company subsequently released atomoxetine into the market during the first quarter of 2003. Atomoxetine was originally known as tomoxetine, however the name was changed to avoid confusion with the drug tamoxifen. Atomoxetine has been shown to be safe and efficacious in children $\geq$ 6 yrs, adolescents, and adults with diagnosed ADHD. This article will focus on the pharmacology, pharmacokinetics, clinical trials, dosage, administration, toxicity, safety, and clinical applications of atomoxetine.

Pharmacology and Pharmacokinetics

The mechanism by which atomoxetine reduces the symptoms of ADHD is unknown. Unlike the stimulants methylphenidate and amphetamine which work primarily on dopaminergic neurons, atomoxetine affects noradrenergic neurons. Pharmacodynamic studies in rats have demonstrated that atomoxetine increases norepinephrine in the prefrontal cortex, a region of the brain involved in attention and memory.[6] The R(-) isomer of atomoxetine inhibits the reuptake of norepinephrine by selectively inhibiting the presynaptic norepinephrine transporter.

Oral administration of atomoxetine results in rapid absorption from the GI tract. Food does not affect the area under the curve (AUC) of atomoxetine, but reduces the peak plasma concentration (C_{max}) by 37% and prolongs the time to maximum concentration (T_{max}) by 3 hours. Normal T_{max} of atomoxetine occurs in 1-2 hours. Atomoxetine is highly protein-bound (98%) to albumin. The volume of distribution is approximately 0.85 L/kg.

First pass metabolism of atomoxetine occurs via the CYP450 2D6 isoenzyme. Genetic polymorphisms of this enzyme exist, with individuals described as extensive metabolizers (EM) or poor metabolizers (PM). Poor metabolizers of CYP2D6 (7% of Caucasians and 2% of African Americans) have impaired activity of this pathway, resulting in increased serum levels of atomoxetine.[7] Coadministration of atomoxetine with inhibitors of CYP2D6 (SSRIs, TCAs, amiodarone, cimetidine, anti-psychotics) may result in increases in the serum concentration of atomoxetine. Dosage adjustment may be warranted. Eighty percent of atomoxetine is excreted in the urine as the inactive metabolite, 4-hydroxyatomoxetine-O-glucuronide. Approximately 17% of atomoxetine is eliminated in the feces as this metabolite.

Clinical Trials

Numerous clinical trials have examined the efficacy of atomoxetine in reducing the symptoms of ADHD. Michelson and colleagues conducted a dose range finding study,[8] as well as, compared once daily dosing of atomoxetine vs. placebo in pa-

Table 1. Summary of Strattera™ clinical trials

Authors	Study Design	N	Age	Dose	Primary Outcome	Significance
Michelson et al. 2001[8]	8-wk R, PC	297	8-18	0.5, 1.2, and 1.8 mg/kg/d bid	Mean change in the ADHD RS vs. placebo	Atomoxetine 1.2 and 1.8 mg/kg/day superior to placebo
Michelson et al. 2002[9]	6-wk R, PC	171	6-16	1.0-1.5 mg/kg/d qd	Mean change in the ADHD RS vs. placebo	Superior outcomes in atomoxetine treated group vs. placebo
Biederman et al. 2002[10]	9-wk R, PC	52	7-13	Max. 2.0 mg/kg/d divided bid	Mean change in the ADHD RS vs. placebo	Superior outcomes in atomoxetine treated group vs. placebo
Michelson et al. 2003[11]	10-wk R, PC	536	41 (average)	Max. 120 mg/d divided bid	Sum of the investigator-rated CAARS values	Superior outcomes in atomoxetine treated group vs. placebo

N=number of patients, R=randomized, PC=placebo-controlled, bid=twice daily, ADHD=attention-deficit/hyperactivity disorder, RS=rating scale-parent version, qd=once daily, CAARS=Conners' adult attention-deficit/hyperactivity disorder rating scale.

tients with ADHD.[9] Other studies have also demonstrated atomoxetine's efficacy in reducing symptoms of ADHD in school-aged girls[10] and adults.[11] Available clinical trials are presented in Table 1.

Michelson and colleagues[8] conducted a randomized, placebo-controlled, dose-response study that examined the relative efficacy of 3 different doses of atomoxetine vs. placebo in 297 children and adolescents between the ages of 8-18 who had ADHD. Patients were randomized to receive either placebo or atomoxetine dosed by weight at 0.5 mg/kg/day, 1.2 mg/kg/day, or 1.8 mg/kg/day for 8 weeks. The study medication was administered in equally divided doses in the morning and late afternoon. The primary outcome was the change in total score in the ADHD rating scale-parent version (RS), an 18-item scale based on a semi-structured interview with the patient's parent or caregiver. Atomoxetine doses of 1.2 mg/kg/day and 1.8 mg/kg/day resulted in nearly identical improvements in ADHD symptoms that were superior to placebo. The atomoxetine dose of 0.5 mg/kg/day did not provide significant reduction in the symptoms of ADHD compared with placebo. This study suggests that an atomoxetine dose of 1.2 mg/kg/day is equally effective to a dose of 1.8 mg/kg/day, and is likely to be the target dose for most patients.

Michelson and colleagues[9] also conducted a randomized, multi-center, placebo-controlled study that assessed the efficacy of once-daily atomoxetine dosing in 171 children and adolescents aged 6-16 with ADHD. Patients were randomized to receive a single dose of placebo or atomoxetine every morning for 6 weeks. Patients in the atomoxetine treatment arm were started at a dose of 0.5 mg/kg/day and were titrated to a target dose of 1.0 mg/kg/day by the end of the first week of treatment. The primary outcome measured in this study was improvement in the ADHD RS. This study also utilized teachers' observations of patients to determine the efficacy of once daily dosing of atomoxetine. Mean reductions in the ADHD RS were significant for the atomoxetine group beginning in week one and lasted for the remainder of the study.

Biederman and colleagues[10] conducted two identical, double-blind, placebo-controlled, multicenter trials were a total of 52 girls with ADHD between the ages of 7-13 were followed for a period of 9 weeks. Patients were divided into two groups based on their previous psychostimulant treatment. The stimulant naive subgroup was randomized to receive atomoxetine, placebo, or methylphenidate. Patients who had previous psychostimulant exposure were randomized to receive either atomoxetine or placebo. The atomoxetine dose was titrated based on clinical response to a maximum daily dose of 2.0 mg/kg/day or 90 mg/day. Patients randomized to the atomoxetine treatment group were given atomoxetine in two daily doses (morning and late afternoon). The primary outcome was improvement in the ADHD RS. Significant improvement in the symptoms of ADHD was demonstrated in the atomoxetine treatment groups beginning one week after randomization, and continuing for the remainder of the trial. Due to a relatively small sample size in the methylphenidate treatment arm, efficacy comparisons were not made between methylphenidate and atomoxetine.

Table 2. Common adverse events associated with the use of Strattera™ in acute (<10 wks) adult trials

Adverse Event System Organ Class/Adverse Event	Percentage of Patients Reporting Event	
	Strattera (n=269)	Placebo (n=263)
Cardiac Disorders		
Palpitations	4	1
Gastrointestinal Disorders		
Constipation	10	4
Xerostomia	21	6
Dyspepsia	6	4
Flatulence	2	1
Nausea	12	5
General Disorders		
Fatigue/lethargy	7	4
Pyrexia	3	2
Rigors	3	1
Weight decreased	2	1
Metabolism/Nutritional Disorders		
Appetite decreased	10	3
Musculoskeletal/Connective Tissue/Bone Disorders		
Myalgia	3	2
Nervous System Disorders		
Dizziness	6	2
Headache	17	17
Insomnia	16	8
Paresthesia	4	2
Sinus headache	3	1
Psychiatric Disorders		
Abnormal dreams	4	3
Libido decreased	6	2
Sleep disorder	4	2
Renal/Urinary Disorders		
Urinary hesitation and/or urinary retention	8	0

Atomoxetine's efficacy was also evaluated in two identical, placebo-controlled studies that randomized 536 adults with ADHD to a 10-week treatment with either placebo or atomoxetine given twice daily.[11] Patients in the atomoxetine group were started on a dose of 60 mg/day, with dosage increases to 90 mg/day after 2 weeks, and 120 mg/day after 4 weeks based on clinical response. Atomoxetine was administered in the morning and late afternoon in two equally divided doses. The primary outcome was a repeated measures, mixed model analysis of post-baseline values of the Conners' adult attention-deficit/hyperactivity disorder rating scale (CAARS). In both studies, atomoxetine was superior to placebo in reducing the symptoms of ADHD in adults.

Toxicity and Safety

Initial atomoxetine safety trials spanned a period of over one year and included over 2067 children and 270 adults. The most common adverse events reported by patients were nausea/vomiting (10-30%), anorexia (2-14%), and dizziness (6%). The most common reasons for therapy discontinuation were increased heart rate and elevated blood pressure, which occurred in 4% of patients. A complete comparison of adverse events reported in $\geq$ 1% of adults are listed in Table 2.

Long-term studies are not available to characterize the effect of atomoxetine on physical growth in pediatric patients. However, short-term studies (up to 9 weeks) of atomoxetine have shown that up to 3.5% of body weight can be lost. Height

and weight should be monitored in all children and adolescents who are taking atomoxetine or any other drug indicated for attention-deficit/ hyperactivity disorder. An interruption in therapy should be considered in any child who exhibits growth inhibition.

Dosage and Administration

Treatment of ADHD in children, adolescents, and adults with oral atomoxetine should be individualized based on a patient's clinical response. The lowest effective dose of atomoxetine is recommended and periodic assessment of patient response should be charted. In patients weighing > 70 kg (including children > 6 years of age, adolescents, and adults) atomoxetine should be initiated at 40 mg/day in 1-2 divided doses. After 3 days, atomoxetine may be titrated up to 80 mg/day. If necessary, the dose may be increased to 100 mg/day and given in 1-2 divided doses.[12] In children and adolescents weighing < 70 kg, atomoxetine should be initiated at 0.5 mg/kg/day in 1-2 divided doses. If well tolerated, dose may be increased after 3 days up to a maximum dose of 1.2 mg/kg/day in 1-2 divided doses. Doses > 1.2 mg/kg/day are not associated with increased clinical response.[12]

Cost

In a survey of three retail pharmacies in the Gainesville area, the cost of a month supply or sixty 40 mg capsules of Strattera™ ranged from $187.99-$207.89 with an average cost of approximately $196.72.

Summary

Atomoxetine is currently the only non-stimulant agent approved by the Food and Drug Administration that is available for the treatment of attention-deficit/hyperactivity disorder. Atomoxetine is a non-scheduled, non-habit forming drug with a low potential for abuse. Clinical trials have demonstrated atomoxetine's superiority over placebo in reducing the symptoms of ADHD in children, adolescents, and adults. Whether long-term treatment with atomoxetine inhibits growth in children and adolescents remains unknown. Until extended safety trials are published, patients requiring long-term therapy with atomoxetine should be routinely monitored and consideration should be given to interrupting therapy in patients who exhibit below average growth. Clinical trials have yet to be performed comparing the efficacy and safety of atomoxetine to the FDA-approved stimulants methylphenidate and amphetamine. Atomoxetine appears to be a safe and efficacious ADHD treatment option for patients and clinicians.

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