Increasingly physicians are using Atomoxetine known as Strattera as the only non-stimulant for the treatment of ADHD. Since ADHD is the most frequently diagnosed psychological disorder in children and Atomoxetine is also the only approved medication for ADHD treatment in adults, you might want to familiarize yourself with the following information. FYI

Helping Hearts Heal

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Atomoxetine, a Novel Treatment for Attention-Deficit-Hyperactivity Disorder

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Abstract and Introduction

Abstract

Atomoxetine is the first nonstimulant drug approved by the United States Food and Drug Administration (FDA) for the treatment of attention-deficit-hyperactivity disorder (ADHD), and the only agent approved by the FDA for the treatment of ADHD in adults. Atomoxetine is a norepinephrine transport inhibitor that acts almost exclusively on the noradrenergic pathway. Its mechanism of action in the control and maintenance of ADHD symptoms is thought to be through the highly specific presynaptic inhibition of norepinephrine. Clinical trials to evaluate the short-term effects of atomoxetine in children and adults have shown that atomoxetine is effective in maintaining control of ADHD. Likewise, long-term trials have determined that atomoxetine is effective in preventing relapse of ADHD symptoms without an increase in adverse effects. A comparative trial of atomoxetine with methylphenidate in school-aged children indicated similar safety and efficacy without the abuse liability associated with some psychostimulants. The most commonly reported adverse effects in children and adolescents are dyspepsia, nausea, vomiting, decreased appetite, and weight loss. The rates of adverse events in the trials were similar for both the once- and twice-daily dosing regimens. The discontinuation rate was 3.5% in patients treated with atomoxetine versus 1.4% for placebo and appeared to be dose dependent, with a higher percentage of discontinuation at dosages greater than 1.5 mg/kg/day. In clinical trials involving adults, the emergence of clinically significant or intolerable adverse events was low. The most common adverse events in adults were dry mouth, insomnia, nausea, decreased appetite, constipation, urinary retention or difficulties with micturition, erectile disturbance, dysmenorrhea, dizziness, and decreased libido. Sexual dysfunction occurred in approximately 2% of patients treated with atomoxetine. Atomoxetine should be used with

caution in patients who have hypertension or any significant cardiovascular disorder. Overall, atomoxetine therapy in patients with ADHD appears to be effective in controlling symptoms and maintaining remission, with the advantages being comparable efficacy with that of methylphenidate, a favorable safety profile, and non-controlled substance status. Additional long-term studies are needed to determine its continued efficacy for those who require lifelong treatment, and comparative trials against other stimulant and nonstimulant agents.

Introduction

Attention-deficit-hyperactivity disorder (ADHD) is the most frequently diagnosed neurobehavioral childhood disorder. Although estimates vary, in the United States ADHD occurs at estimated rates of 3-7% in school-aged children and 6% in adults.[1, 2] The number of cases continues to grow each year, and the disorder was identified as a serious public health problem by the Centers for Disease Control and Prevention in 1999.[3] Children often exhibit symptoms of aggressiveness, inattention, hyperactivity, inability to concentrate at school, and difficulty in the completion of simple tasks.[4] The main impairments caused by ADHD are through academic and social dysfunction.[3] Developmental problems such as in reading, spelling, and arithmetic are common as well.[5] Children with ADHD often have trouble communicating appropriately, and 10-54% have speech problems as a result.[5] These impairments may lead to demoralization and poor self-esteem in children, thus causing increased rates of high-risk injuries, tobacco addiction, and substance abuse.[3] Typically, ADHD is diagnosed in boys more often than in girls, possibly because of the observations that boys exhibit much more aggressive behavior and symptoms than do girls.[4]

Childhood ADHD was once believed to be a disorder that would dissipate once the child entered into early adulthood. However, follow-up studies reveal that 10-60% of children with ADHD continue to have symptoms as they become adults.[6] Adults with persistent symptoms of ADHD may experience occupational and vocational dysfunction, continued social impairment, and increased rates of motor-vehicle accidents.[3] Controversy continues to surround the diagnosis and classification of ADHD in adults. Scientifically, the diagnosis is based on the criteria for ADHD as set by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR).[1] However, as the symptoms of ADHD manifest less frequently with age, some researchers may argue that the criteria for diagnosis of ADHD listed in the DSM-IV-TR are too stringent for adults, since adults must exhibit symptoms in at least two settings.[3] Typically, adults with ADHD exhibit their symptoms strongest in the workplace, whereas symptoms experienced at home may be less recognizable.[7] Adults who express difficulty organizing their finances, completing household chores, or keeping appointments on time may dismiss these behaviors as a personality trait rather than relating them to similar behaviors exhibited at work and associating their condition with ADHD.

Although the intensity and severity of symptoms will decline over time, adults with ADHD find dealing with everyday situations challenging and complex. Time management and work execution become very complicated tasks, whereas they may be

observed as simple functions to the adult without ADHD.[7] An issue that continues to further complicate the recognition of ADHD is that no single cause has been identified. Various hypotheses have been presented and are used as a basis to define treatment, such as prenatal and perinatal risk factors, genetics, and neurobiologic deficits that include decreased frontal cortical activity and decreased extracellular dopamine activity.[3]

Traditionally, the pharmacologic treatments of choice for ADHD have been psychostimulant agents such as methylphenidate or dextroamphetamine. Most research suggests that stimulants work to alleviate the symptoms of ADHD through the potentiation of dopamine and, to a lesser extent, norepinephrine in the central nervous system.[8] However, approximately 30% of children and adults with ADHD either do not respond to or do not tolerate psychostimulants.[9] Although the existing psychostimulants have established efficacy, safety, and a generally favorable adverse-effect profile, the existence of patients who do not respond and the prospect of long-term pharmacotherapy, as well as the potential for drug abuse or diversion, have gener-ated support for the development and use of nonstimulant agents for the treatment of ADHD.

Research has shown that the noradrenergic neurotransmitter system is involved with visual attention, sustainment of attention for long periods of time, initiation of an adaptive response, and learning and memory.[10] In the past, agents that have noradrenergic and/or dopaminergic effects have demonstrated benefit in the treatment of ADHD.[11, 12] Although not approved by the United States Food and Drug Administration (FDA) for treatment of ADHD, antidepressants, particularly the tricyclic antidepressants, have been found to be effective in treating ADHD because of their inhibition of norepinephrine reuptake.[8] However, the risk of serious adverse effects and the availability of alternative agents have tempered the use of tricyclic antidepressants by patients with ADHD or depression.[3, 9] Based on the mechanism of action of the tricyclic antidepressants in the inhibition of norepinephrine reuptake (a noradrenergic component thought to be depleted in the prefrontal cortex of humans with ADHD), the development of newer therapies has focused on increasing the levels of norepinephrine in an attempt to control symptoms of ADHD.[8] Evidence arising from pharmacologic studies targeting the noradrenergic hypothesis has led to the development of an agent that specifically targets the norepinephrine transporter; this agent is atomoxetine.

Atomoxetine (Strattera; Eli Lilly and Co., Indianapolis, IN), a norepinephrine transport inhibitor, was developed as an antidepressant. It now is the first nonstimulant agent approved by the FDA for treatment of ADHD in children and adults. The drug was originally known generically as tomoxetine, but this designation was changed to avoid potential prescribing and dispensing errors due to confusion with similar sounding agents (e.g., tamoxifen).

Mechanism of Action

The precise mechanism of action of atomoxetine in ADHD is unknown. Unlike traditional stimulant agents currently approved for ADHD in children and adults that work through increasing systemic levels of dopamine by binding to dopamine receptors

in the brain, atomoxetine exerts its pharmacologic effect by the selective inhibition of the presynaptic norepinephrine transporter, therefore inhibiting the reuptake of norepinephrine. In the brain, the primary noradrenergic region is the locus ceruleus, an area that induces an alert waking state and enhances informational processing and attention to environmental stimuli.[13] In animal studies, the increased levels of dopamine and norepinephrine in the prefrontal cortex are necessary for optimal functioning.[8] Deficits of these neurotransmitters in the right dorsal prefrontal cortex affect attention regulation and inhibition to the response of distracting stimuli, whereas deficits in the right orbital prefrontal cortex are associated with immature behavior, lack of restraint, and increased motor activity.[8] In one study conducted in rats, atomoxetine increased extracellular levels of norepinephrine and dopamine in the prefrontal cortex of the brain 3-fold without concurrent increases in serotonin.[14] This study also found that atomoxetine did not increase the levels of dopamine in the striatum or nucleus accumbens, an action exerted by traditional psychostimulants, therefore suggesting that atomoxetine might pose a lower risk for drug abuse. Atomoxetine appears to have little affinity for other major neurotransmitter systems such as cholinergic, histaminergic, serotonergic, or β-adrenergic systems.[15]

Pharmacokinetic Profile

Absorption and Distribution

Atomoxetine is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration. Significant differences are noted in the disposition of atomoxetine between extensive metabolizers of cytochrome P450 (CYP) 2D6 substrates and genetically poor metabolizers. For example, the absolute bioavailability of atomoxetine in extensive metabolizers is 63%, whereas the bioavailability in poor metabolizers is 94%.[16] In single- and multiple-dose studies, the maximum concentration (C_{max}) of atomoxetine was reached in 1-2 hours after dosing in extensive metabolizers and 3-4 hours in poor metabolizers.[17, 18]

The administration of atomoxetine after ingestion of a standardized high-fat meal did not affect the extent of absorption, but it did decrease the rate of absorption.[16] This resulted in a 37% lower C_{max} and a delayed time to C_{max} by approximately 3 hours.[16] In poor metabolizers, the steady-state concentration of atomoxetine in plasma is 3-fold higher with multiple doses compared with that with a single dose.[17] In pharmacokinetic studies comparing both once- and twice-daily dosing in extensive metabolizers, the steady-state profiles in patients who received twice-daily dosing were similar to those in patients who received once-daily dosing, indicating that peak plasma concentrations were not increased with twice-daily dosing.[18]

The distribution of atomoxetine is primarily into total body water, with a volume of distribution of 0.85 L/kg. Atomoxetine is approximately 98% protein bound, whereas the active metabolite 4-hydroxyatomoxetine is approximately 67% protein bound.[19]

Metabolism and Excretion

The metabolic pathways of atomoxetine are depicted in Figure 1. Atomoxetine is metabolized predominantly in the liver by the CYP enzymes, primarily the CYP2D6 isoenzyme. The degree of CYP2D6 metabolism in children is similar to that in adults, indicating that maturation of the enzyme has reached adult competency in children aged 7-14 years.[18] The primary mechanism of clearance is by oxidative metabolism and glucoronidation in extensive metabolizers, based on several single- and multiple-dose pharmacokinetic studies.[16, 19, 20] Most metabolites are eliminated renally. There are three major phase 1 metabolic pathways that atomoxetine undergoes: aromatic ring hydroxylation, benzylic oxidation, and N-demethylation.[17, 19] The primary phase 1 metabolite that is formed from the oxidative processes is 4-hydroxyatomoxetine, which is further conjugated to 4-hydroxyatomoxetine-*O*-glucuronide, the primary active metabolite of atomoxetine (Figure 1). The metabolite 4-hydroxyatomoxetine appears to be as pharmacologically active as the parent compound in terms of norepinephrine transport inhibition, with a decreased blockade of the serotonin transporter. However, in pediatric pharmacokinetic studies, levels of 4-hydroxyatomoxetine were very low compared with atomoxetine, suggesting that it has a minor role in norepinephrine transporter blockade after administration of atomoxetine.[18] Another phase 1 metabolite, *N*-desmethylatomoxetine, is formed by the enzymatic pathway CYP2C19 and is considerably less pharmacologically active than 4-hydroxyatomoxetine.[19] It therefore does not contribute significantly to the efficacy of atomoxetine. Low plasma concentrations were observed in extensive metabolizers, most likely because of the subsequent oxidative metabolism of *N*-desmethylatomoxetine.[19] However, if the rate of metabolic oxidation is slowed, the primary pathway for elimination is through *N*-demethylation, resulting in accumulation of *N*-desmethylatomoxetine.[16, 19, 20]

The mean elimination half-life of atomoxetine after oral administration is 5.2 hours.[16] In poor metabolizers, the mean elimination half-life is 21.6 hours, a result of reduced clearance of atomoxetine (Table 1). This results in an area under the concentration-time curve (AUC) that is about 10-fold greater and a steady-state C_{max} that is approximately 5-fold greater than those of extensive metabolizers.[16] The elimination half-life of the metabolite 4-hydroxyatomoxetine is 6-8 hours in extensive metabolizers, whereas the elimination half-life of *N*-desmethylatomoxetine is 34-40 hours in poor metabolizers.[16] Greater than 80% of the dose of atomoxetine is excreted primarily in the urine as 4-hydroxyatomoxetine. Seventeen percent of the total dose is excreted through the feces. Less than 3% of the dose is excreted unchanged, indicating extensive biotransformation.[16]

Extensive versus Poor Metabolizers. Results of studies performed in healthy adults indicate that the pharmacokinetics of atomoxetine are influenced by the genetic polymorphism of CYP2D6.[19] Atomoxetine undergoes bimodal distribution with two distinct populations that are characteristic of the CYP2D6 enzyme: extensive metabolizers and poor metabolizers.[17, 19, 20] Only 7% of the Caucasian population and less than 1% of the Asian population are considered poor metabolizers.[21] These individuals have either a mutation or a deletion of the CYP2D6 gene; therefore, efficient metabolism of CYP2D6 substrates is not achieved. Patients who may be suspected of

being poor metabolizers are identified through genotyping procedures that specify metabolic status.

The circulating plasma concentrations of 4-hydroxyatomoxetine may vary at about 1% of the atomoxetine concentration in extensive metabolizers and 0.1% of the atomoxetine concentration in poor metabolizers.[16] Although 4-hydroxyatomoxetine is formed primarily by CYP2D6 in poor metabolizers, the metabolite also may be formed by other enzymatic pathways.[20, 22] There is a potential for drug accumulation during multiple dosing in patients who show the polymorphic characteristic of poor metabolizers. Pharmacokinetic studies indicate that individuals who are poor metabolizers display a higher steady-state concentration of atomoxetine and *N*-desmethylatomoxetine than that of extensive metabolizers.[18]

In a single-dose pharmacokinetic study conducted in extensive metabolizers, in which the atomoxetine dose was 10 mg, the plasma concentrations and AUC values of the metabolites were much lower than the atomoxetine concentration.[18] Even though the concentration of 4-hydroxyatomoxetine was measurable in plasma, it was still 26 times less than the concentration of atomoxetine. In multiple-dose pharmacokinetic studies conducted in extensive metabolizers in which the dosage was 20-45 mg twice/day, the degree of accumulation of atomoxetine or its metabolites at steady-state concentrations was low, as the half-life, clearance, and volume of distribution were similar to those of single-dosing pharmacokinetics.[18] The plasma concentration of 4-hydroxyatomoxetine was 35 times lower than the concentration of atomoxetine. With combination of both the single- and multiple-dose pharmacokinetics, a linear regression analysis indicated that the concentration of atomoxetine in the plasma was proportionate to the dose and not related to the dosing schedule. As doses are increased on a mg/kg basis, the AUC for atomoxetine increases proportionately.

Clinical Trials

The safety and efficacy of atomoxetine were established in six pivotal, randomized, double-blind, placebo-controlled trials and in one open-label comparative trial against methylphenidate.[23-27] These are the largest studies to date evaluating the treatment of ADHD in children and adults. The clinical trials are summarized in Table 2.[23-33]

Dose-Ranging Studies in Children and Adolescents

In five trials, atomoxetine was evaluated in children and adolescents with ADHD.[23-26] The data from two of the trials were presented together, as the trials were identically designed.[25] One trial was an open-label trial comparing atomoxetine with methylphenidate.[26]

The investigators in the first trial evaluated atomoxetine twice/day in children and adolescents (aged 8-18 yrs) with ADHD.[23] In this multicenter study, the investigators also evaluated the effects of atomoxetine in poor metabolizers by performing phenotypic testing to analyze for the CYP2D6 genotype in all enrolled subjects. Two hundred ninety-

seven participants were enrolled, of which 71% were boys and 29% were girls. In approximately 67% of patients, the diagnosis was for the mixed subtype ADHD (both inattentive and hyperactivity-impulsivity types); 38% had the psychiatric comorbid opposition defiance disorder (ODD). Participants were eligible if they met the DSM-IV-TR criteria for ADHD by clinical assessment and confirmed by a structured interview using the behavioral module of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime versions (KSADS-PL) and by a symptom severity score at least 1.5 standard deviations above the age and sex norms on the ADHD Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHD Rating Scale) for the total score or for either of the inattention or hyperactivity-impulsivity subscales. Exclusion criteria were an IQ less than 80, a serious medical illness, comorbid bipolar disorder or any history of psychosis, history of a seizure disorder, ongoing use of any psychoactive drug other than the study drug, and a history of substance abuse within the previous 3 months.

The primary outcome was an improvement in the symptoms of ADHD assessed with the ADHD Rating Scale and defined by a mean change in the total score from baseline to end point. The hyperactivity-impulsivity and inattention subscales of the ADHD Rating Scale, the Conners' Parent Rating Scale-Revised (CPRS-R) short form, and the Clinical Global Impressions of Severity (CGI-S) assessed secondary outcomes. The Children's Depression Rating Scale-Revised (CDRS-R) was used to assess affective symptoms, whereas the Child Health Questionnaire assessed the change in the subject's social and family functioning. Safety and tolerability were assessed through open-ended questions concerning adverse effects that occurred, as well as regular monitoring of vital signs and laboratory data.

Atomoxetine dosages were 0.5, 1.2, and 1.8 mg/kg/day. After being assessed for depression and anxiety using the KSADS-PL depression and anxiety models, patients were randomly assigned to receive placebo or one of the three dosages of atomoxetine for approximately 8 weeks. All patients in the atomoxetine arm began therapy at 0.5 mg/kg/day, and the dosages of those assigned to the higher dosage arms were later titrated with intermittent steps of 0.8 and 1.2 mg/kg/day at 1-week intervals.

Atomoxetine was determined to be superior to placebo on the primary outcome measure of an improvement in ADHD symptoms in those patients assigned to receive 1.2 and 1.8 mg/kg/day ($p < 0.05$). No difference was noted between the 1.2- and 1.8-mg/kg/day dosages as indicated by the change in ADHD Rating Scale scores. Similar outcomes were seen in the secondary end points of a reduction in the scores of the inattention and hyperactivity-impulsivity subscales, the CGI-S, and the CPRS-R scores. Symptom reduction was the same in children compared with adolescents as seen in ADHD Rating Scale scores. However, older children and adolescents had a significant response to 0.5 mg/kg/day compared with placebo as seen by a mean reduction in ADHD Rating Scale scores ($p < 0.05$). Reduction of affective symptoms, measured by the CDRS-R, was greater between the two higher dosages compared with placebo, as indicated by a change in score (1.2 mg/kg/day group -1.5, 1.8 mg/kg/day group -2.0, placebo group +1.1,

p<0.05). Also, improvements in social and family functioning were superior for all atomoxetine dose groups compared with those in the placebo group.

Seventeen participants classified as CYP2D6 poor metabolizers were randomized to treatment. The mean change in the improvement of ADHD Rating Scale scores was the same between the poor and extensive metabolizers. This indicates that dosing adjustments are not necessary in patients classified as poor metabolizers.

The safety and tolerability of atomoxetine were favorable for all dosages. No statistically significant differences were seen in adverse events between the 1.2- and 1.8-mg/kg/day groups. A dose-response effect was suggested with somnolence and anorexia but did not prove to be statistically significant.

The time to onset of effect with atomoxetine at the varying dosages was not assessed. The 0.5-mg/kg/day arm included about half of the patients, as in the other two higher dose treatment arms the dosages were titrated upward, in an attempt by the investigators to provide evidence of a dose-response effect and a threshold dosage for drug effect rather than for efficacy of atomoxetine. This, however, may affect the internal validity of the study as a comparison of dosages in the determination of the primary outcome, as a decrease in ADHD symptoms, may be skewed to reflect that the lower dosage of atomoxetine may not be as effective as the higher dosages. As such, the study data suggest that there is an effect on the symptoms of ADHD with atomoxetine 0.5 mg/kg/day, but that there is a graded response as the dosage is titrated upward. Based on the results of this study, there does not appear to be a greater improvement in symptoms beyond the 1.2-mg/kg/day dosage, although the 1.8-mg/kg/day dosage was well tolerated.

A second trial[24] performed by the same group of investigators was a dose-ranging study to evaluate the efficacy of once-daily administration of atomoxetine in participants aged 6-16 years who met the same criteria for diagnosis and assessment of ADHD as those in the previous study. The primary objective was to provide evidence that atomoxetine was effective for the treatment of ADHD when given once/day, as measured by a change in the total score of ADHD Rating Scale from baseline to end of study (response > 25% reduction from baseline in total score on the ADHD Rating Scale). Secondary end points were a reduction in the ADHD Rating Scale subscales of inattention and hyperactivity-impulsivity, and a reduction in CPRS-R, Conners' Teacher Rating Scale-Revised (CTRS-R), CGI-S, and a change in family and social behavior as assessed by a parent-rated diary developed specifically for this study. Patients were excluded if they had a history of substance abuse (> 3 mo), a serious medical illness, comorbid bipolar disorder or any history of psychosis, history of a seizure disorder, or ongoing use of a psychoactive drug other than the study drug.

One hundred seventy-one patients were randomly assigned to receive either atomoxetine or placebo; of these 171 patients, 70.6% were boys and 29.4% were girls. One assigned patient did not receive any drug and therefore was excluded from all analyses. Fifty-five percent of patients in the atomoxetine arm had ADHD of the mixed subtype. The most common comorbid psychiatric disorder was ODD, occurring in 18.8% of the patients in

the atomoxetine arm. Fifty-five percent of the patients in the total population had been treated with a stimulant. The treatment period was 6 weeks.

Patients in the atomoxetine arm were started at 0.5 mg/kg/day for 3 days, then the dosage was increased to 0.75 mg/kg/day for the remainder of the week. After the first week, the dosage was increased to 1.0 mg/kg/day for 4 weeks, when efficacy was assessed by using the CGI-S scale to determine severity of symptoms. Those who had a score greater than two, indicating more than minimal symptoms, had a further dosage increase to 1.5 mg/kg/day, which remained as the maximum dosage throughout the study. In addition to using the CGI-S score, efficacy was measured by using the ADHD Rating Scale, the CPRS-R, the CTRS-R, and a 13-item parent-rated diary developed by the investigators to assess the efficacy of atomoxetine during the evening and early morning periods. The safety and tolerability of the two dosages were assessed through the use of open-ended questions and frequent monitoring of vital signs.

Overall improvement seen in the ADHD Rating Scale total score indicated that treatment with atomoxetine was superior to placebo, with a 59.5% response in the atomoxetine group versus 31.3% in the placebo group when comparing scores from baseline to end point. Secondary efficacy was achieved by the reduction in the mean changes of the CGI-S score from baseline and in the mean change in score of the CPRS-R ($p<0.001$ for both measures), indicating that atomoxetine was superior to placebo ($p=0.003$), with 28.6% of atomoxetine-treated patients demonstrating a reduction of symptoms versus 9.6% of patients taking placebo. Atomoxetine significantly reduced the CTRS-R scores as well ($p=0.016$). No significant differences were seen in the parent ratings of offspring behavior, suggesting interuser variability when assessing symptoms and questioning objectivity of the results. Statistical significance was shown for atomoxetine in only two items -- inattention and distractibility in the evening ($p=0.003$), and difficulty settling at bedtime ($p=0.03$) -- suggesting that the drug may decrease evening symptoms.

The most important finding of the study was the clinically significant effects of atomoxetine on symptom control throughout the day. Despite its relatively short plasma half-life (approximately 4 hrs in extensive metabolizers), the duration of effect of atomoxetine persisted into the evening after a once-daily dose was given in the morning. This effect was seen in the individual analysis of the symptom of inattention from the daily diary, suggesting a drug-specific benefit occurring late in the day and early evening. Unfortunately, a comparative twice-daily dosing arm was not included to determine the relative efficacy of once-daily versus twice-daily dosing. Evaluation of these data might suggest that once-daily dosing may be as effective as twice-daily dosing in producing symptom reduction; however, adequately sized direct comparisons are needed before definitive conclusions can be drawn.

Another group of authors presents evidence that once-daily atomoxetine therapy provides continuous symptom relief throughout the day when given as a single daily dose in the morning.[28] Their study, performed in children aged 6-12 years, demonstrated that atomoxetine 1.3 mg/kg/day was significantly more effective than placebo in reducing the core symptoms of ADHD by about 40% in atomoxetine-treated patients versus 17% in

placebo-treated patients (total score ADHD Rating Scale, p<0.05). Likewise, continued efficacy in reducing ADHD symptoms into the evening hours and through the night was determined through evaluation of Daily Parent Ratings of Evening and Morning Behavior-Revised (DPREMB-R) scores (a reduction in the total score of 44% for atomoxetine-treated patients vs 29% reduction in placebo-treated patients). The DPREMB-R total score decrease for the atomoxetine group during the first week of treatment was significantly different from that of the placebo group after 1 day of treatment, indicating a rapid onset of effect at a dosage of 0.8 mg/kg/day (p<0.001).

The third and fourth trials to evaluate atomoxetine in children and adolescents were conducted by the same group.[25] The two identical randomized, double-blind, placebo-controlled, proof-of-concept trials were run in parallel and evaluated the efficacy of atomoxetine at a maximum dosage of 2.0 mg/kg/day, admin-istered twice/day. A smaller methylphenidate treatment arm was used in the event that atomoxetine showed no difference from placebo. The study period was 12 weeks, which included an additional 2-week drug washout period and a 1-week drug discontinuation period. The primary objective was to determine the possibility of atomoxetine as an alternative to stimulant therapy.

Two hundred ninety-one patients aged 7-12 years were randomly assigned to receive atomoxetine (65 patients in trial 1, 64 in trial 2), methylphenidate (20 in trial 1, 18 in trial 2), or placebo (62 in trial 1, 62 in trial 2). In both trials, 81% of the patients were boys and 19% were girls. Inclusion criteria were slightly different from those of previous studies. Patients needed to meet the DSM-IV-TR criteria for ADHD of the inattentive type confirmed by a clinical interview using the KSADS-Episodic:ADHD, and a symptom severity score greater than 1.5 standard deviations above age and sex norms on the ADHD Rating Scale. There was one major difference from enrollment of other studies. Whereas previous studies included patients who were CYP2D6 poor metabolizers, this study excluded any patient who had a CYP2D6 poor metabolizer genotype. Other exclusion criteria were a history of substance abuse, a serious medical illness, comorbid bipolar disorder or any history of psychosis, history of seizure disorder, and weight less than 25 kg.

Participants were stratified into two arms: one arm comprised patients with prior treatment with a psychostimulant, the other arm comprised patients with no prior psychostimulant treatment. Those who had been stratified to the previous psychostimulant arm received either atomoxetine or placebo; the patients in the other arm, without previous psychostimulant treatment, were randomly assigned to receive atomoxetine, methylphenidate, or placebo.

Primary efficacy was achieved as a reduction in the total ADHD Rating Scale score for all patients in the comparison of atomoxetine with placebo (trials 1 and 2, p<0.001). No significant differences in efficacy were noted between methylphenidate and atomoxetine when given to stimulant-naïve patients. In addition, atomoxetine achieved significance in reduction of ADHD Rating Scale total score for patients previously treated with a stimulant (trial 1, p<0.001; trial 2, p=0.048) and in reduction of inattention (trials 1 and 2,

p<0.001) and hyperactivity-impulsivity (trial 1, p<0.001; trial 2, p=0.002) subscales of the ADHD Rating Scale, compared with placebo. Secondary efficacy was achieved for atomoxetine in the reduction of the CGI-S score for both studies (trial 1, p=0.003;trial 2, p=0.001). All patients treated with atomoxetine were classified as responders, defined by a 25% or greater reduction in ADHD Rating Scale scores (trial I, atomoxetine 61.4% vs placebo 24.6%, p<0.001; trial 2, atomoxetine 58.7% vs placebo 40.0%, p=0.048). This indicated that selective inhibition of norepi-nephrine transport would provide a reduction in ADHD symptoms in school-aged children and a nonstimulant option for ADHD treatment.

These studies demonstrate that atomoxetine is effective in children and adolescents, when compared with placebo, for the treatment of ADHD. Interpreting the possible comparative efficacy of atomoxetine with that of methylphenidate is difficult, as the use of methylphenidate in these studies was intended to validate the study design in the event that atomoxetine showed no difference from placebo. Also, whether the frequency of adverse effects was increased at the higher dosages of atomoxetine was not reported.

A number of post hoc analyses from the two proof-of-concept studies[25] have examined the efficacy of atomoxetine in children with comorbid ODD, children who had failed psychostimulant therapy, children with ADHD of the inattentive type, and girls with ADHD.[29-32] All analyses were favorable for atomoxetine in reducing symptoms of ADHD. In the analysis involving children with comorbid ODD, the reduction in symptoms associated with ODD with atomoxetine was not statistically significant. The results of the studies are summarized in Table 2.[23-33]

Comparative Study in Children and Adolescents

A prospective, randomized, open-label trial assessed the comparability of atomoxetine and methylphenidate for 10 weeks in children and adolescents.[26] The data reported are from a relapse-prevention study in which previous responders to stimulant ADHD therapy were enrolled to determine how a nonstimulant therapy would compare with the traditional stimulant therapy. This study enrolled boys aged 7-15 years and girls aged 7-9 years who met the DSM-IV-TR diagnostic criteria for ADHD. After an evaluation and washout period, patients were randomly assigned to receive open-label treatment with either atomoxetine or methylphenidate for 10 weeks. The study enrolled 228 patients. Randomization was based on a 3:1 ratio (atomoxetine:methylphenidate) with a block size of four for the first four patients. For the remaining patients, randomization was based on a 5:1 ratio with a block size of six. Block randomization was used to provide a balance for the early treatment phase and provide room for internal decision making.

At study entry, patients were tested to determine whether they were poor or extensive metabolizers through the analysis of DNA taken from whole-blood samples for CYP2D6 poor metabolizer alleles. Patients determined to be poor metabolizers were started at a lower dosage of 0.2 mg/kg/day, with the dosage titrated to a maximum of 1.0 mg/kg/day. The dosage for the extensive metabolizers was titrated to a maximum of 2.0 mg/kg/day. Patients assigned to the methylphenidate arm were started at 5 mg 1-3 times/day, with

dosage titration based on the investigators' clinical assessment of patient response and tolerability. The maximum daily dosage of methylphenidate was 60 mg/day.

No differences were noted between the groups for the study's primary and secondary end points. Primary efficacy was defined by a total change in ADHD Rating Scale score from baseline to the end of the study period. Secondary efficacy was defined as a reduction of the total ADHD Rating Scale (parent), CPRS-R, CTRS-R, and CGI-S (ADHD subscale).

No girls were assigned to the methylphenidate arm and only 17 were assigned to the atomoxetine arm. The small sample (44 patients) treated with methylphenidate limited the comparability of effects between atomoxetine and methylphenidate, although the lack of significant differences noted in the outcomes suggest that the two are not different in terms of efficacy. The smaller size of the methylphenidate arm will inflate any effects seen, thus allowing the data to appear comparative to atomoxetine for effect. Larger studies with comparable sample sizes between the atomoxetine and methylphenidate arms may clearly show the superiority of one agent over the other in efficacy. In addition, a gradual dose-titration design as well as the varying schedule of methylphenidate dosing at once/day to 3 times/day confound the time and dose effects of the two therapies, therefore making it impossible to assess for onset of effect for both groups. Effects of methylphenidate may be seen earlier in treatment based on its pharmacologic effect. In patients with severe ADHD, use of a pharmacologic agent that has a proved rapid time to effect may be more favorable to an agent that may take longer before a clinical effect is seen. The final mean dosage of methylphenidate was 18.7 mg/day, which for most patients may be an average dosage for maintenance of ADHD.

By study end, the average dosage of atomoxetine in the poor metabolizer group was one third of the dosage in the extensive metabolizer group (approximately 0.5 vs 1.5 mg/kg/day). The rate of adverse effects was not larger in the poor metabolizer group than in the extensive metabolizer group; however, the small sample of poor metabolizers limits the interpretability of these results. Previous studies with larger populations of poor metabolizers evaluated similar dosages of atomoxetine and determined that the safety and tolerability of these dosages are similar for both groups.[23]

The study was open-label; therefore, bias may have been introduced by the investigator and parent assessments of symptoms based on their expectations of the treatment. In addition, the groups were not well matched in terms of sex, in that there were significantly more boys than girls for each group and no girls were randomly assigned to the methylphenidate group. Bias also may have been introduced into the results for atomoxetine as it is thought that girls with ADHD do not exhibit as aggressive of symptoms as do boys and therefore may appear to respond more favorably to treatment. Comparison with a stimulant may show greater reduction in symptoms based on previous results evaluating the efficacy of methylphenidate. Finally, the effects of either treatment on school behavior in comparison to home behavior are questionable, owing to the lack of direct teacher assessments. Conclusions drawn from improvements in school functioning are based on parent reports, the validity of which was not confirmed.

Placebo-Controlled, Efficacy Studies in Adults

Two identical trials conducted by the same group evaluated the efficacy of atomoxetine in adults older than 18 years.[27] These were double-blind, placebo-controlled, phase III trials to assess the efficacy of atomoxetine 60-120 mg/day given in two doses for 10 weeks. Two hundred eighty participants were enrolled and randomly assigned to receive atomoxetine or placebo in trial 1. Two hundred fifty-six patients were enrolled in trial 2. In trial 1, 64% of patients were men and 36% were women; in trial 2 66% were men and 34% were women. Patients were eligible if they had moderate-to-severe symptoms of ADHD based on the Conners' Adult ADHD Diagnostic Interview (CAARS-INV) for the DSM-IV-TR. Exclusion criteria were a history of substance abuse (previous 3 mo), a serious medical illness, comorbid depression or bipolar disorder or any history of psychosis or anxiety, ongoing use of psychoactive drugs other than the study drug, hypo- or hyperthyroidism, and a history of a seizure disorder.

Primary efficacy was defined as changes in the total and subscale scores of the CAARS-INV from baseline to end of study. A significant reduction was achieved in the total CAARS-INV score at study end for both trials (trial 1, $p=0.062$; trial 2, $p=0.002$) in patients treated with atomoxetine. For the inattention (trial 1, $p=0.010$; trial 2, $p=0.001$) and hyperactivity-impulsivity (trial 1, $p=0.017$; trial 2, $p=0.012$) subscales of the CAARS-INV, a significant reduction in scores indicated the superiority of atomoxetine over placebo for an improvement of these symptoms in both trials. Secondary efficacy was defined and achieved in both trials as a change in the total and subscale scores of the patient-rated tests: the CAARS-Self (trial 1, $p=0.003$; trial 2, $p=0.008$), CGI-S (trial 1, $p=0.011$; trial 2, $p=0.002$), and the Wender-Reimherr Adult Attention Deficit Disorder Scale (trial 1, $p=0.001$; trial 2, $p=0.041$) for atomoxetine over placebo. Significant differences were not found in trial 1 concerning improvements in social, family, and work functions as measured by the Sheehan Disability Scale total and domain scores. In trial 2, however, a significant difference was noted in the improvements of social, family, and work functioning for the total ($p=0.022$) and the domain ($p=0.007$) scores. This indicates that treatment with atomoxetine in adults with ADHD may improve quality of life by improving social and work functioning; however, future studies will be required to truly determine this effect. Limitations to the study include the lack of a comparative arm with a stimulant, such as methylphenidate, to evaluate treatment efficacy against the standard therapy in this population.

Precautions and Contraindications

Cardiovascular Effects

Based on the pharmacologic effects of increased levels of norepinephrine in the body, atomoxetine should be used with caution in patients who have hypertension, tachycardia, or any other significant cardiovascular or cerebrovascular disease because of its effects on increasing blood pressure and pulse. In clinical studies performed in children, adolescents, and adults, the quantitative increases in blood pressure observed were clinically insignificant for systolic and diastolic blood pressure and pulse.[23, 24, 27] Any

increases were sustained within 1 year from baseline to end point, with a mean systolic increase of 3.6 mm Hg and a mean diastolic increase of 3.5 mm Hg.[16] Mean increase in the pulse during 1 year was 3.9 beats/minute.[16] As treatment continued, the increased changes in blood pressure ceased to occur. Once atomoxetine was discontinued, the blood pressure quickly returned to baseline.[6, 23, 24, 34]

Regarding electrocardiographic changes, no statistically significant changes were reported. Trials evaluating the increases in blood pressure and pulse in adults indicated that moderate increases from baseline to end point were not found to be clinically significant. In clinical trials involving adult patients with ADHD, mean increases in pulse in subjects treated with atomoxetine occurred at about 5 beats/minute more compared with the mean pulse rate of placebo-treated subjects. The frequency of clinically observed tachycardia was about 3% and 0.8% in atomoxetine- and placebo-treated groups, respectively, and was dose dependent.[16] The increases in pulse observed subsided on discontinuation of atomoxetine. Mean increases in blood pressure were about 1.5 mm Hg in systolic and diastolic blood pressures in pediatric atomoxetine-treated patients and about 3 mm Hg in systolic and about 1 mm Hg in diastolic blood pressures in adult atomoxetine-treated patients. Systolic measurements greater than 150 mm Hg were not found to be statistically significant and occurred at a rate of 1.9% and 1.2% in subjects treated with atomoxetine versus placebo, respectively.[16]

Urinary Outflow

In trials evaluating the effects of atomoxetine in adults with ADHD, the rate of urinary retention or hesitation was 3% in a sample of 269 atomoxetine-treated patients versus 0% in the placebo group.[16] Therefore any complaint of urinary retention or hesitancy should be considered possibly related to atomoxetine.

Special Populations

Patients With Hepatic Insufficiency

Pharmacokinetic studies to evaluate the concentration of atomoxetine in extensive metabolizers showed a 2-fold increased AUC in patients with moderate hepatic insufficiency (based on Child-Pugh class B) and a 4-fold increased AUC in patients with severe hepatic insufficiency (based on Child-Pugh class C) compared with healthy subjects. A reduction in the initial and target doses by 50% and 25% of the normal dose for patients who have moderate hepatic insufficiency and for those with severe hepatic insufficiency, respectively, is recommended.[16, 17]

Patients With Renal Insufficiency

In extensive metabolizers with end-stage renal disease, the extent of systemic exposure of atomoxetine was 65% higher than that of healthy subjects. However, a clinically significant difference was not noted when doses were decreased on a mg/kg basis.

Therefore, no dosing adjustments are recommended for extensive metabolizers who have mild, moderate, or end-stage renal disease when using the normal dosing regimen.[16]

Children and the Elderly

No formal studies are available that evaluate atomoxetine treatment in children younger than 6 years. The pharmacokinetic values of atomoxetine in children 6 years and older have been found to be similar to that of adults. Efficacy beyond 9 weeks of therapy and safety beyond 1 year of therapy have not been studied.

No formal studies are available that evaluate the safety and efficacy of atomoxetine in patients older than 65 years.

Pregnant and Lactating Women

Atomoxetine is classified as pregnancy category C. In rabbit studies, a dose of 100 mg/kg, approximately 23 times the maximum human dose on a mg/m^2 basis, produced a decrease in live fetuses and an increase in resorption in one of three studies. In these studies, the no-effect dose observed was 30 mg/kg.[16]

No adequate, well-controlled studies are available that evaluate atomoxetine therapy in pregnant women. Therefore, treatment with atomoxetine should be recommended only when the benefits outweigh the risks of treatment. The effect of atomoxetine on labor and delivery in humans is not known.

Atomoxetine and/or its metabolites were found to be excreted in the milk of rats. No studies are available that evaluate the amount of atomoxetine or its metabolites in the milk of nursing women. Therefore, the risks versus the benefits should be considered if atomoxetine is to be used for the treatment of ADHD in nursing women.[16]

Adverse Effects

A total of 2067 pediatric patients and 267 adult patients treated with atomoxetine or placebo in clinical trials were evaluated for adverse effects occurring with the agent. Throughout the trials, no deaths were reported as a result of treatment with atomoxetine, and discontinuation rates as a result of adverse effects were low. In the 2067 children and adolescents treated with either placebo or atomoxetine, the most commonly occurring adverse events were gastrointestinal (e.g., dyspepsia, nausea, vomiting, abdominal pain, decreased appetite) and central nervous system effects (e.g., fatigue, dizziness, mood swings, headache, insomnia). Weight loss also occurred as a result of decreased appetite; however, few trials reported this as an adverse event.[34] The adverse-event rates in the trials were similar for both the once-daily and twice-daily dosing regimens.[16, 34]

Overall, the tolerability of atomoxetine in clinical trials has been favorable, with most events occurring and dissipating throughout therapy. The most commonly occurring adverse events observed in short-term (< 9 wks) clinical trials evaluating both once- and

twice-daily dosing in pediatric patients were gastrointestinal and central nervous system effects. These events occurred at a rate greater than 5% for both once- and twice-daily dosing of atomoxetine versus placebo.[16] No significant differences were seen in the relationship between the dose of atomoxetine and the adverse event.

The rate of discontinuation was 3.5% in patients treated with atomoxetine and 1.4% for the placebo groups in the placebo-controlled trials.[16] In most studies evaluating atomoxetine's effects in poor and extensive metabolizers, the rate of discontinuation due to adverse effects was approximately 5% for extensive metabolizers and 7% for poor metabolizers.[16] Occurrence of adverse events appears to be dose dependent, with a higher percentage of discontinuations at dosages of atomoxetine greater than 1.5 mg/kg/day.[16]

In clinical trials involving adults, the emergence of clinically significant, intolerable adverse events was low. The most commonly observed adverse events were dry mouth, insomnia, nausea, decreased appetite, constipation, urinary retention or difficulties with micturition, erectile disturbance, dysmenorrhea, dizziness, and decreased libido. Sexual dysfunction occurred in about 2% of patients treated with atomoxetine.[16] The most commonly reported events were erectile disturbance, impotence, and abnormal orgasms. The rate of discontinuation was 8.5% for atomoxetine-treated patients and 3.4% for placebo-treated patients.[16]

Drug Interactions

Atomoxetine is metabolized primarily to an active metabolite, 4-hydroxyatomoxetine, by CYP2D6. Genetically poor metabolizers of this isoenzyme (5-10% of the United States population) may have an extended elimination (half-life approaching 20 hrs) that may necessitate dosage adjustments. In vitro studies have shown that atomoxetine is an inhibitor of both the CYP2D6 and CYP3A4 enzymes, but not CYP1A2 or CYP2C9.[35] Yet, studies performed in vivo in a population of extensive metabolizers demonstrate that atomoxetine administered at the maximum recommended dosage will not inhibit the clearance of drugs metabolized by CYP2D6.[35] In addition, studies performed to evaluate atomoxetine in poor metabolizers demonstrate that atomoxetine administered at the maximum recommended dosage will not likely inhibit the clearance of or induce the metabolism of CYP3A4 substrates.[35] However, one study demonstrated an increase in the steady-state plasma concentrations of atomoxetine with a prolonged half-life after exposure to a potent CYP2D6 inhibitor (e.g., fluoxetine, paroxetine) that was similar to atomoxetine plasma concentrations observed in poor metabolizers.[36] Note that combination therapy with ADHD drugs is common because of the high rate of comorbid psychiatric conditions. Combining pharmacotherapy is commonplace, although conventional psychostimulants (e.g., methylphenidate) pose little interaction liability; however, caution should be exercised when using amphetamine compounds with other sympathomimetic agents.[37] Atomoxetine should not be used in patients who receive therapy with a monoamine oxidase inhibitor or within the first 14 days after discontinuation of therapy.

Potential for Abuse

A comparison of the behavioral effects of atomoxetine versus methylphenidate in those who take recreational drugs was published recently.[38] Drug users subjectively reported the effects of the two agents through the use of a visual analog scale (VAS) assessing behavior, the Addiction Research Center Inventory-Short Form (ACRI), and the Adjective Rating Scale (ARS). The Digit Symbol Substitution Test was used to demonstrate psychomotor performance of patients taking atomoxetine and methylphenidate. The results indicated that patients taking methylphenidate exhibited a significantly higher pleasurable effect and were more stimulated than were patients taking placebo. Patients taking atomoxetine associated the agent with the "bad" or "sick" components of the VAS when compared with placebo ($p<0.05$). No significant differences were noted between atomoxetine and placebo along the domains of the ACRI and the ARS, whereas patients taking methylphenidate had significantly higher scores than those of patients taking placebo ($p<0.05$).

These results indicate that atomoxetine does not induce the same subjective effects as methylphenidate. The mechanism of action of atomoxetine differs from stimulants in that it inhibits norepinephrine transporters, whereas stimulants increase levels of dopamine. Therefore, the potential for diversion or abuse with atomoxetine is unlikely compared with stimulants, making atomoxetine a good alternative for patients in whom substance abuse potential is high.

In clinical trials, atomoxetine did not appear to promote the development of new tics or exacerbation of comorbid anxiety. Therefore, in patients who are not able to take stimulants because of contraindications related to tics or anxiety, atomoxetine may be a reasonable alternative. Trials are under way to evaluate the efficacy of atomoxetine in reducing the symptoms of ADHD in patients with comorbid tics or anxiety.

Dosing and Administration

Atomoxetine is indicated for the long-term treatment of ADHD in children, adolescents, and adults. Some advantages for the use of atomoxetine over stimulants are that atomoxetine may be given without regard to meals and does not need to be tapered on discontinuation. Based on pediatric pharmacokinetic data, atomoxetine may be dosed on a milligram/kilogram basis in pediatric patients owing to its proportionality of dose-to-plasma concentration effect. For children weighing less than 70 kg, initial dosages should be 0.5 mg/kg/day. Atomoxetine may be given either as a single dose or in divided doses because of the drug's rapid absorption and elimination, which result in steady-state profiles that are similar to single-dose profiles. Dosages should be titrated after 3 days of initial therapy to a target daily dose of approximately 1.2 mg/kg. The maximum recommended daily dose in children is 1.4 mg/kg or 100 mg, whichever is less, owing to the lack of significance in producing a greater reduction of symptoms for dosages greater 1.4 mg/kg/day. For patients who are treated concomitantly with a strong CYP2D6 inhibitor (e.g., paroxetine, fluoxetine, quinidine), atomoxetine should be started at 0.5 mg/kg/day and cautiously increased to a maximum dosage of 1.2 mg/kg/day if after 4

weeks of therapy the patient does not improve clinically. In studies to evaluate atomoxetine in children, efficacy was not assessed in those weighing less than 25 kg; therefore, caution should be exercised when beginning therapy, and patients should be monitored closely for adverse events during titration.

For children, adolescents, and adults weighing more than 70 kg, the initial dosage should be at 40 mg/day either in divided doses or as a single daily dose in the morning. Titration should occur after 3 days of therapy to a target dosage of 80 mg/day. Like antidepressants, the full benefit of atomoxetine may not be seen until about the fourth week of therapy. Dosages may be further titrated if clinical efficacy is not achieved, to a maximum dosage of 100 mg/day. If the use of a strong CYP2D6 inhibitor (e.g., paroxetine, fluoxetine, quinidine) is in place, atomoxetine should be started at 40 mg/day and cautiously increased to a maximum dosage of 80 mg/day if the patient does not exhibit a clinical response after 4 weeks of therapy. Doses greater than 120 mg or total daily doses above 150 mg have not been formally evaluated for safety. Patients should be assessed periodically for the continued maintenance of ADHD symptoms if atomoxetine is to be used long term. Discontinuation of atomoxetine may occur at any time throughout therapy without tapering.[16]

Summary

Atomoxetine is approved by the FDA for the treatment of ADHD in children, adolescents, and adults and has been proved effective for controlling symptoms that last throughout the day and into the evening. Data suggest that atomoxetine is effective in children and adolescents with ADHD of the mixed subtype, as well as with concomitant ODD. It is a reasonable alternative to stimulants in those who do not respond to treatment or in patients who are unable to tolerate stimulants. In addition, atomoxetine treatment has been proved effective in adults with a new diagnosis of ADHD or in those adults with ADHD who are unable to tolerate a stimulant. An added benefit of atomoxetine is its noncontrolled status, making it convenient for parents acquiring supplies of the drug for more than 1 month and favorable for patients with a high abuse potential. Additional advantages with atomoxetine are persistent symptom control into the evening, a decreased risk of user rebound, and a lower risk of induction of tics and psychosis.

Tables

Table 1. Pharmacokinetic Differences Between Extensive and Poor Metabolizers[16, 19]

Parameter	Extensive Metabolizers	Poor Metabolizers
Bioavailability (%)	63	94
T_{max} (hrs)	1-2	3-4

Half-life (hrs)	5.2	21.6		

Primary metabolites		
4-Hydroxyatomoxetine-*O*-glucuronide		
Half-life (hrs)	6-8	--
AUC (μg•hour/ml)[a]	2.74	0.935
N-desmethylatomoxetine		
Half-life (hrs)	--	34-40
AUC (μg•hour/ml)[a]	0.618	2.82

T_{max} = time to maximum concentration; AUC = area under the concentration-time curve.
[a]Based on parameters produced by multiple 20-mg doses of atomoxetine administered twice/day.[19]

Table 2. Summary of Clinical Trials of Atomoxetine

Study Design	No. of Pts, M/F (%), Age (yrs)	Treatment	Efficacy Measures	Results
Child and adolescent studies				
Randomized, double-blind, placebo-controlled, multicenter; duration 8 wks[23]	297 71/29 8-18	ATOM 0.5 mg/kg/day (n=44) ATOM 1.2 mg/kg/day (n=84) ATOM 1.8 mg/kg/day (n=85) Placebo (n=84) Given twice/day	ADHD RS total score, inattention, and hyperactivity-impulsivity; CPRS-R ADHD, hyperactive, cognitive, oppositional; CGI-S, CDRS-R, CHQ-PF50, psychosocial summary	Significant reduction in ADHD RS total score, inattention, hyperactivity-impulsivity, CPRS-R, CDRS-R (p<0.05)
Randomized, double-blind,	171[a] 71/29	ATOM 1.0-1.5	ADHD RS total score, inattention,	Significant reduction in ADHD RS total

placebo-controlled, multicenter; duration 6 wks[24]	6-16	mg/kd/day (n=85) Placebo (n=85) Given once/day	and hyperactivity-impulsivity; CPRS-R ADHD, hyperactive, cognitive; CGI-S, CDRS-R, psychosocial summary, CTRS-R. DPREMB, ADHDRS-IV-Parent: Inv total score	score (p<0.001), inattention, hyperactivity-impulsivity, CPRS-R, CDRS-R (p<0.05), oppositional Significant improvements in behavior at school by reductions in CTRS (p=0.02) Significant improvement in inattention and distractibility in the afternoon (p=0.003) and in less difficulty settling down at bedtime (p=0.023) by the DPREMB
Randomized, double-blind, placebo-controlled, multicenter; duration 12 wks[25]	147 81/19 7-12	ATOM 1.3-2.0 mg/kg/day (n=65) MPH (n=20) Placebo (n=62)	ADHD RS total score, inattention, and hyperactivity-impulsivity; CPRS-R ADHD, hyperactive, cognitive, oppositional; CGI-S,CDRS-R, psychosocial summary	Significant reduction in ADHD RS total score (p<0.001) for non-stimulant-naïve patients and for stimulant-naïve patients (p=0.001 ATOM, p<0.001 MPH; no significant differences between ATOM and MPH) Significant reduction in inattention and hyperactivity-impulsivity subscale for ATOM (p<0.001)
Randomized, double-blind, placebo-controlled, multicenter; duration 12 wks[25]	144 81/19 7-12	ATOM 1.3-2.0 mg/kg/day (n=64) MPH (n =18) Placebo	ADHD RS total score, inattention, and hyperactivity-impulsivity; CPRS-R ADHD, hyperactive, cognitive,	Significant reduction in ADHD RS total score (p<0.001) for non-stimulant-naïve patients and for stimulant-naïve patients (p=0.001

		(n=62)	oppositional; CGI-S, CDRS-R, psychosocial summary	ATOM, $p<0.001$ MPH; no significant differences between ATOM and MPH) Significant reduction in inattention ($p<0.001$) and hyperactivity-impulsivity subscale for ATOM ($p=0.002$)
Randomized, open-label, multicenter; duration 10 wks[26]	228 91/9 M 7-15 F 7-9	ATOM 1-2 mg/kg/day (n=184) MPH maximum dosage 60 mg/day (n=44)	ADHD RS total score, inattention, and hyperactivity-impulsivity; CPRS-R ADHD, hyperactive, cognitive, oppositional; CGI-S, CDRS-R, psychosocial summary	Significant reductions in ADHD RS total score, inattention, hyperactivity-impulsivity subscales in both ATOM and MPH groups ($p=0.001$) No significant differences between ATOM and MPH
Randomized, double-blind, placebo-controlled, multicenter; duration 6 wks[28]	197 66/34 6-12	ATOM 0.8-1.8 (n=133) Placebo (n=64) Given once/day	ADHDRS-IV-Parent: Inv total score, DPREMB-R, CGI-Parent-Evening, CGI-ADHD-S	Significant reduction in ADHDRS-IV-Parent: Inv total score ($p<0.05$) with ATOM 1.3 mg/kg/day for the treatment of core symptoms Efficacy of ATOM was greater for symptom suppression into the evening hours as seen as a reduction of DPREMB-R and CGI-Parent-Evening scores ($p<0.001$) Significant reduction in the CGI-ADHD-S ($p<0.001$) seen in ATOM-treated patients

				Significant reduction of morning symptoms ($p<0.05$) and evening symptoms ($p<0.01$) as seen in the DPREMB-R Significant reduction in DPREMB-R total score for the ATOM group vs placebo after the first day of treatment indicating a rapid onset of effect ($p<0.001$)
Adult studies				
Randomized, double-blind, placebo-controlled, multicenter; duration 10 wks[27]	280 64/36 > 18	ATOM 60-120 mg/day in divided doses (n=141) Placebo (n=139)	CAARS-Inv, CAARS-Self, WRAADDS, HAM-A, HAM-D, Sheehan Disability	Significant reduction in CAARS-Inv total ($p=0.006$), CAARS-Inv inattention score ($p=0.010$) and CAARS-Inv hyperactivity-impulsivity ($p=0.017$)
Randomized, double-blind, placebo-controlled, multicenter; duration 10 wks[27]	256 66/34 > 18	ATOM 60-120 mg/day in divided doses (n=129) Placebo (n=127)	CAARS-Inv, CAARS-Self, WRAADDS, HAM-A, HAM-D, Sheehan Disability	Significant reduction in CAARS-Inv total ($p=0.002$), CAARS-Inv inattention score ($p=0.001$) and CAARS-Inv hyperactivity-impulsivity ($p=0.012$)
Post hoc analysis				
Pooled analysis of two trials: efficacy of ATOM in children with ADHD who have comorbid ODD; duration 9	98 79/21 7-12	ATOM 1.3-2.0 mg/kg (n=53) Placebo (n=45)	ADHD RS total score, inattention, and hyperactivity-impulsivity; CPRS-R ADHD, hyperactive, cognitive, oppositional; CGI-	Significant reduction in ADHD RS total score ($p<0.001$) Significant reduction in inattention ($p<0.001$) and hyperactivity-impulsivity subscale

wks[25, 29]				S, CDRS-R, psychosocial summary	for ATOM (p=0.002) Reduction in CPRS-R (ADHD index, p=0.005), in CPRS-R (cognitive index, p=0.006), and in CPRS-R (hyperactive subscale, p=0.003) Nonsignificant reduction in ODD subscale Significant reduction in CGI-S (p=0.003)
Pooled analysis of two trials: efficacy of ATOM in children with ADHD who had previously failed stimulant therapy; duration 9 wks[25, 30]	33 81/19 7-12	ATOM 1.3-2.0 mg/kg (n=14) Placebo (n=19)		ADHD RS total score, inattention, and hyperactivity-impulsivity; CPRS-R ADHD, CGI-ADHD-S	Significant reduction in ADHD RS total score (p=0.027) Significant reduction in inattention (p=0.048) and hyperactivity-impulsivity subscale for ATOM (p=0.025) Significant reductions in CPRS-R (p=0.029) and CGI-S (p=0.017)
Pooled analysis of two trials: efficacy of ATOM in children with ADHD of the inattentive subtype; duration 9 wks[25, 31]	48 78/22 7-12	ATOM 1.3-2.0 mg/kg (n=24) Placebo (n=24)		ADHD RS total score, inattention, and hyperactivity-impulsivity; CPRS-R ADHD, CGI-ADHD-S	Significant reduction in ADHD RS total score (p=0.003) Significant reduction in inattention (p=0.012) and hyperactivity-impulsivity subscale for ATOM (p=0.007) Significant reduction in inattention score achieved in the first week of ATOM treatment and maintained through

				study end Significant reductions in CPRS-R (p=0.009) and CGI-S (p=0.027)
Pooled analysis of two trials: efficacy of ATOM in school-aged girls with ADHD; duration 9 wks[25, 32]	52 0/100 7-12	ATOM 1.3-2.0 mg/kg (n=31) Placebo (n=21)	ADHD RS total score, inattention, and hyperactivity-impulsivity; CPRS-R ADHD, CGI-ADHD-S, WISC-IQ	Significant reduction in ADHD RS total score (p=0.002) Significant reduction in inattention (p=0.001) and hyperactivity-impulsivity subscale for ATOM (p=0.006) Significant reduction in ADHD RS total score achieved in first week and maintained until study end (p<0.05) Significant reductions in CPRS-R (p<0.001) and CGI-S (p<0.001)
Pooled analysis of two double-blind, placebo-controlled studies and four open-label studies; duration 10 wks[33]	NA	ATOM 0.5-1.8 mg/kg/day given twice/day	ADHD RS total score, adverse events, weight, vitals, ECGs	Greater reduction in ADHD RS total scores in PMs vs EMs (p=0.003), which was also greater than placebo (p<0.001) in the fixed-dose study Significant reduction seen in the combined open-label trials in a reduction of the ADHD RS total score forPMs vs EMs (p<0.001) No significant differences in data-corrected QT interval between EMs and PMs

				Significant reductions in weight (p<0.001) and increases in pulse (p<0.001) seen in PMs vs EMs No significant changes in BP observed between PMs and EMs Frequency of headache greater in EMs vs PMs (p<0.046) All other adverse events were similar between both groups No serious safety concerns noted between both groups Efficacy may be greater in PMs than EMs No dosage adjustment is required in PMs when treating with ATOM

ATOM = atomoxetine; ADHD = attention-deficit-hyperactivity disorder; ADHD RS = ADHD Rating Scale; CPRS-R = Conners' Parent Rating Scale-Revised; CGI-S = Clinical Global Impressions of Severity; CDRS-R = Children's Depression Rating Scale-Revised (affective symptoms of child's condition); CHQ-PF50 = Child Health Questionnaire (parent-rated health outcome scale to measure physical and psychosocial well being of child and family functioning); CTRS-R = Conners' Teacher Rating Scale-Revised; DPREMB-R = Daily Parent Ratings of Evening and Morning Behavior; MPH = methylphenidate; MASC = Multidimensional Anxiety Scale for Children; CAARS-Inv = Conners' Adult ADHD Rating Scale-Investigator; WRAADDS = Wender-Reimherr Adult Attention Deficit Disorder Scale; HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Scale; WISC-IQ = Wechsler Intelligence Scale for Children-Third Edition; ODD = opposition defiance disorder; NA = not available; ECG = electrocardiogram; PM = poor metabolizer; EM = extensive metabolizer; BP = blood pressure.

ªOne patient did not receive any study drug and was excluded from the analysis.

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