Atomoxetine: a novel treatment for child and adult ADHD

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Abstract: Attention deficit hyperactivity disorder (ADHD) is a common chronic condition with childhood onset that can continue into adulthood. Medication is a fundamental element in the management of this disorder. Atomoxetine is the newest nonstimulant medication approved by the United States Food and Drug Administration (FDA) for the treatment of ADHD. It is the only nonstimulant medication approved by the FDA for treatment of adult ADHD. Atomoxetine is a norepinephrine reuptake inhibitor that selectively inhibits the presynaptic norepinephrine transporter. A growing body of literature supports the use of atomoxetine both in children and adults with ADHD. This paper summarizes information from the literature about atomoxetine, including pharmacokinetics, pharmacodynamics, clinical trials, dosing, and side-effects.

Keywords: atomoxetine, ADHD, review, nonstimulants

Introduction

Attention deficit hyperactivity disorder (ADHD) is a childhood onset psychiatric disorder that occurs in 3%–7% of children, with an unknown but lower prevalence in adults. The disorder can result in significant psychosocial dysfunction in academic performance, occupational success, and social interactions. The patient with ADHD is also at increased risk for a number of comorbidities including oppositional defiant disorder, conduct disorder, depression, anxiety, and substance abuse (APA 2000) Dysfunction in the transmission of dopamine and norepinephrine has been detected in this disorder and medications that target the catecholaminergic system have been identified as efficacious for treatment (Spencer, Biederman, et al 2002).

Atomoxetine was originally named tomoxetine, with initial research completed for an indication of the treatment of major depression (Zerbe et al 1985). Phase III trials were completed and initial data suggested it was a potentially effective treatment for depressive illness. However, development of the drug for the treatment of depression was discontinued in 1990 for unclear reasons. In 1996, the medication was re-presented as a potential treatment for ADHD (Preti 2002). The medication was renamed atomoxetine to avoid confusion with the cancer drug tamoxifen.

Atomoxetine is the newest nonstimulant medication for the treatment of ADHD and the first nonstimulant with an indication from the Federal Drug Administration (FDA) for the management of ADHD in children over 6 years of age, adolescents, and adults. Stimulant medications are effective for up to 80% of patients with ADHD, but a portion of patients do not respond or are unable to tolerate problematic side-effects (Wilens and Spencer 2000). In addition, the possibility of misuse may be a concern, especially in patients with a history of substance abuse. Atomoxetine presents an alternative medication in the treatment of this disorder. This paper reviews information about atomoxetine including pharmacology, open and blinded clinical trials, case reports, dosage and administration, and safety profile.

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Pharmacology

Pharmacokinetics

Atomoxetine is absorbed through the gastrointestinal tract with peak levels in 1.83 hours in pediatric patients and 1–1.5 hours in adult patients. A high fat meal decreases the rate of absorption but has no effect on the amount of absorption. Peak levels with a high fat meal are at about 4–4.5 hours. Once absorbed, 99% of the medication is bound to albumin. The active metabolite, 4-hydroxyatomoxetine, is about 67% protein bound. The medication is primarily distributed into total body water. Comparison of once-daily and twice-daily dosing does not demonstrate differences in steady-state profiles. Atomoxetine is not an inducer or inhibitor of any cytochrome P 450 system. It is metabolized to active 4-hydroxyatomoxetine by the CYP isoenzyme 2D6. This metabolite is rapidly made inactive by glucuronidation. It is excreted in the urine (80%) and feces (17%), with the remaining amount excreted as unchanged atomoxetine (Eli Lilly 2003).

Approximately 7% of Caucasians, 1% of Asians (Poolsup et al 2000), and a variable percentage of blacks (Wennerholm et al 1999) are poor metabolizers for CYP isoenzyme 2D6. Thus, in certain populations there may be significant alterations in pharmacokinetics. The half-life of atomoxetine has been found to range from 5.2 hours in rapid metabolizers to 21.6 hours in slow metabolizers. The half-life of the active metabolite, 4-hydroxyatomoxetine, has been found to range from 6 to 8 hours in rapid metabolizers, and from 34 to 40 hours in slow metabolizers. The average steady-state plasma concentrations are about 10 times greater in slow metabolizers in comparison with fast metabolizers. Bioavailability has been shown to vary significantly, from 63% in rapid metabolizers to 94% in slow metabolizers (Eli Lilly 2003). Despite these differences in half-life, concentration, and bioavailability, the number and severity of side-effects appear to be similar across 2D6 phenotypes (Sauer et al 2005). Future research will establish if CYP2D6 genotyping will be a useful tool for determining appropriate dosing schedules for patients taking atomoxetine (deLeon et al 2006)

The pharmacokinetics of atomoxetine in the child and adolescent population were studied in 21 patients aged 7–14 identified as extensive metabolizers of CYP2D6. The medication reached peak plasma concentrations 1–2 hours after dosing. Half-life of the medication after a single dose and at steady state ranged from 3.12 to 3.28 hours. These data were noted to be similar to previous studies of atomoxetine in adults, with the conclusion that the 2D6 isoenzymes appeared to be mature in this population (Witcher et al 2003). Earlier studies have suggested that the CYP2D6 system is likely fully developed by several months of age (Kearns 1995). Atomoxetine is also metabolized to the relatively inactive metabolite N-desmethylatomoxetine through the CYP isoenzyme 2C19. However, this is a small portion of the metabolism. Medication effect appears to last significantly longer than the half-life.

Pharmacodynamics

The noradrenergic system is important for sustained attention, learning, memory, and adaptive response. The right dorsal prefrontal cortex is a key system for attention regulation and inhibition (Arnsten et al 1996). Atomoxetine is a specific norepinephrine reuptake inhibitor which functions by selective inhibition of the presynaptic norepinephrine transporter resulting in increased noradrenergic transmission. Extracellular dopamine and norepinephrine have been shown to increase threefold in the prefrontal cortex with atomoxetine in animal models (Bymaster et al 2002). Interestingly, there appears to be no effect on extracellular dopamine levels in the striatum or nucleus accumbens, where drugs of abuse elicit a reward response. This is possibly due to the higher ratio of noradrenaline transporters relative to dopamine transporters in the prefrontal cortex compared with the striatum and nucleus accumbens. The medication appears to have minimal affinity for muscarinic, serotonergic, cholinergic, and adrenergic receptors, and serotonin and dopamine transporters.

In an attempt to better understand the neurobiology of ADHD and the effects of stimulants and atomoxetine, a study examined medication effects on inhibitory and excitatory processes in 9 healthy right-handed adults. Conditioned and unconditioned motor-evoked potential amplitudes were measured with paired and single transcranial magnetic stimulation of the motor cortex. Measurements were completed at 2 visits separated by 1 week. One visit analyzed processes before and after a single dose of methylphenidate 30 mg and 1 visit analyzed processes before and after a single dose of atomoxetine 60 mg. Both medications decreased cortical inhibition and increased cortical facilitation. There were no significant differences in physiologic effects between the two medications (Gilbert et al 2005).

Efficacy studies

The drug development of atomoxetine for the treatment of ADHD in adults, adolescents, and children proceeded methodically, with the initial trials in adults followed by open-label safety trials in children. At this juncture, proof-of-concept trials were conducted in children followed by placebo controlled trials that considered appropriate dosing and then longer-term use. The process used in the development of atomoxetine has been noted to be a positive model for the development of treatments specifically directed towards children and adolescents (Prasad 2005).

Open trials

An open-label trial with 10 male subjects, ages 9–14 was conducted over 10 weeks. Baseline and post-treatment measurements included the ADHD Rating Scale-IV-Parent Version, Clinical Global Impressions-ADHD-Improvement Scale, and Conners Parent Rating Scale-Revised: Short Version. Eight subjects completed the study, with 7 of the 8 demonstrating medication efficacy. One subject withdrew after developing a rash which occurred for a second time when the medication was reintroduced. Six of the 10 subjects had temporary suppression of appetite. Four subjects experienced transient gastrointestinal symptoms, 3 subjects experienced irritability, and 3 subjects experienced fatigue (Kratochvil et al 2001).

An open-label trial with 30 subjects, ages 7–14, was conducted over 11 weeks. Subjects received 1.9 mg/kg daily in 2 divided doses. Eight subjects discontinued treatment with only 2 reporting a side-effect (mild headaches) in conjunction with noncompliance; the other 6 were discontinued in the study for a variety of situational issues (eg, noncompliance, relocation). Response to medication was assessed with the ADHD Rating Scale-IV-Parent Version, Clinical Global Impressions-ADHD-Improvement Scale, and Conners Parent Rating Scale-Revised: Short Version. Of the 22 subjects who completed the trial, 75% were identified as positive responders to medication. Adverse events were reported in 83.3% of subjects. All adverse events were minor and included rhinitis, headache, anorexia, dizziness, nervousness, and somnolence. Increases were noted in blood pressure and heart rate. Electrocardiograms (EKG) did not show any medication effect on conduction, repolarization, or rhythm. Blood chemistries also appeared unaffected by the medication trial. Three patients with comorbid anxiety and 1 patient with comorbid depression demonstrated improved anxiety and depressive symptoms as measured by the Clinical Global Impression-Anxiety Scale and Clinical Global Impression-Major Depression Scale (Spencer et al 2001).

In a randomized, prospective open-label trial, 228 subjects were randomized to atomoxetine treatment (n=184) or methylphenidate treatment (n=44) for 10 weeks. Sixty-six subjects taking atomoxetine discontinued treatment, 10 because of side-effects (5.4%), 10 because of lack of efficacy as perceived by the subject (5.4%), and 19 because of lack of efficacy as perceived by the subject and physician (10.3%). Nineteen subjects taking methylphenidate discontinued treatment, 5 because of side-effects (11.4%), 1 because of lack of efficacy as perceived by the subject (2.3%), and 5 because of lack of efficacy as perceived by the subject and physician (11.4%). Medication response was assessed with the ADHD-IV Rating Scale-parent version only. Both groups demonstrated significant improvements in ADHD symptoms. Statistically significant increases were reported for blood pressure and pulse for both medications. There were no changes on EKG results or blood chemistries. Common adverse events in the atomoxetine treatment group included headache, abdominal pain, anorexia, nervousness, vomiting, somnolence, nausea, and insomnia (Kratochvil et al 2002).

A prospective, open study was completed on 604 children and adolescents at 33 sites in the UK, continental Europe, Israel, South Africa, and Australia for 10 weeks. Symptoms were measured with the ADHD Rating Scale and the Child Health Questionnaire. ADHD scores were found to decrease by 56.7%, with 69% of patients rated as having no or minimal symptoms (Buitelaar et al 2004).

An open trial of atomoxetine was completed on 7 children with ADHD who had previously failed stimulants. The medication was begun at 0.5 mg/kg daily titrating up to 1.4 mg/kg daily at day 4. Behavior was measured with the Hyperactivity Index of the Conners Teacher's Rating Scale. No improvement was seen on this scale after treatment was instituted, although number of weeks on medication was not specified in this trial (Velcea et al 2004).

Results from an ongoing 3-year open label study of 384 adult patients at 31 sites were reported at a period of up to 97 weeks. The Conners' Adult ADHD Rating Scale-Investigator Rated Screening version (CAARS-Inv) was used to assess total ADHD symptoms. Mean CAARS-Inv scores decreased 33.2% from baseline with adverse events including increased heart rate, blood pressure, and a slight decrease in weight (Adler et al 2005).

The predictive potential of the P300 response was assessed for identifying patients who would respond to atomoxetine. Seventeen patients ages 6–17 were administered P300 testing and then completed a trial of atomoxetine. Medication response was measured with the ADHD rating scale-parent version as rated by the investigator. A mean auditory P300 amplitude of 6.8 microV predicted a positive response to atomoxetine with a positive predictive value of 0.88 and a negative predictive value of 0.67 (Sangal et al 2005).

A retrospective chart review was completed on 7 patients with pediatric Bipolar Disorder and ADHD who received treatment with atomoxetine. Six of the 7 patients had a positive response. No patients demonstrated symptoms of hypomania or mania. Side-effects identified included sedation, nausea, and decreased appetite (Hah and Chang 2005).

Controlled trials

Adults

A double-blind, placebo-controlled crossover study of atomoxetine was completed in 22 adults with a diagnosis of ADHD. Thirteen of the 22 patients (59%) had a comorbid psychiatric diagnosis. Patients were treated in 3-week increments with titration up to 80 mg/day by the second week. There was a 1-week washout between treatment periods. An average dose of 76 mg/day was well tolerated. Improvement was established as a 30% reduction on the ADHD Rating Scale which was administered weekly. Eleven patients demonstrated improvement while on atomoxetine while 2 patients demonstrated improvement while on placebo. Improvements were also noted in the Stroop Color Word test and Interference T test. One patient chose to discontinue treatment while on atomoxetine, after developing anxiety and irritability during the second week of the trial. An additional patient developed anxiety, 1 developed anxiety and insomnia, and 3 developed insomnia, all while receiving atomoxetine. While the response rate was described as modest, it was noted to be comparable with adult ADHD response rates to other medications indicated for treatment of ADHD in adults (Spencer et al 1998).

Michelson et al (2003) completed 2 randomized, placebo-controlled studies on the use of atomoxetine in adults with 280 patients at 17 sites in study I and 256 patients at 14 sites in study II. Diagnosis of ADHD was obtained through clinical interview with the Conners' Adult ADHD Diagnostic Interview for DSM-IV. Symptoms were corroborated by a second reporter or with report of childhood symptoms from a parent or older sibling. Symptoms were required to be of at least moderate symptom severity. Most patients were male, with 72% of patients meeting criteria for combined type ADHD. About 27% of patients in both study groups met criteria for ADHD-inattentive type with less than 1% meeting criteria for ADHD-hyperactive–impulsive type. Patients with serious medical illness, mood, anxiety, or psychotic disorders were excluded from the study. Patients had an initial 1-week medication washout phase followed by a 2-week placebo phase. Patients who did not respond in the placebo phase were then randomized to placebo or atomoxetine for a 10-week period. Atomoxetine doses ranged from 60 to 120 mg/day. Symptom improvement was measured with the CAARS Total ADHD Symptom Score. Both studies demonstrated significant reductions in CAARS scores, with study II finding significant improvement in social, family, and work function as measured by the Sheehan Disability Scale (Michelson et al 2003).

A more recent study examined the potential of atomoxetine as a weight-reduction medication. A 12-week, randomized, double-blind, placebo-controlled trial was completed, with 15 obese women receiving atomoxetine (final dose 100 mg/day) and 15 obese women receiving placebo. Measurements included bodyweight, waist circumference, blood pressure, heart rate, fasting plasma glucose and lipids, and depressive symptoms. The atomoxetine group lost significantly more bodyweight than the placebo group ($p<0.0001$) and side-effects were reported as minimal (Gadde et al 2006).

Children and adolescents

The earliest controlled studies in patients under age 18 were completed in 2002 with proof-of-concept studies. The two 12-week studies were stratified, randomized, double-blind, placebo-controlled trials in a combined total of 291 children from age 7 to 12. About one third of the patients met criteria for comorbid oppositional defiant disorder with lesser frequencies of anxiety, mood, and elimination disorders. The study began with a 2-week medication washout period followed by a 9-week acute treatment phase followed by a 1-week drug discontinuation phase. Children with a previous trial of stimulant medication received either atomoxetine or placebo. Children without a previous stimulant trial were randomized to atomoxetine, placebo, or methylphenidate. Mean dose of atomoxetine at the end of the study was 1.5 mg/kg daily. Efficacy was primarily evaluated with the

Table 1 Controlled trials of atomoxetine

Type of Study	Duration (weeks, months)	Number of ADHD patients	Age range of patients (years)	Major findings
Double-blind, placebo, crossover (Spencer et al 1998)	3-wk increments with 1-wk washout between trials	22	Adults	Modest response rate on the ADHD Rating Scale
Randomized, placebo, multisite (Michelson 2003)	1-wk washout phase followed by 2-wk placebo phase followed by 10-wk trial	280	Adults	Significant reduction in CAARS scores
Randomized, placebo, multisite (Michelson et al 2003)	1-wk washout phase followed by 2-wk placebo phase followed by 10-wk trial	256	Adults	Significant reduction in CAARS scores
Stratified, randomized, double-blind, placebo (2 trials) (Spencer, Heiligenstein, et al 2002)	2-wk washout followed by 9-wk treatment phase followed by a 1-wk discontinuation phase	Combined total of 291	At least 7 but less than 13 yrs	Significant reduction in ADHD Rating Scale scores
Double-blind, placebo (Michelson et al 2002)	6 wks	170	6–16 yrs	Significant improvements noted on the ADHD Rating Scale, CGI, and CPRS-short version
Double-blind, placebo, multisite (Michelson et al 2001)	12- to 18-day washout phase followed by 8-wk trial	297	8–18 yrs	Significant improvements noted on the ADHD Rating Scale, CGI
Double-blind, placebo, multisite (Kelsey et al 2004)	8 wks	197	6–12 yrs	Significant improvements noted on the ADHD Rating Scale
Randomized, double-blind, placebo, multi site (Michelson et al 2004)	9 mo	416 patients with prior + response to atomoxetine in an open study	6–15 yrs	Relapse in 22.3% of patients on atomoxetine compared to 37.9% in patients on placebo
Randomized, double-blind, placebo(Newcorn et al 2005)	8 wks	293 patients (39% with comorbid ODD)	8–18 yrs	Significant improvements on the ADHD Rating Scale. Improvements in ODD symptoms at higher dose of atomoxetine
Randomized, placebo, double-blind (Weiss et al 2005)	7 wks	153	8–12 yrs	Significant improvements on Teacher Ratings on the ADHD Rating Scale.
Randomized, placebo, double-blind (Sumner et al 2005)	2 wks of placebo followed by 10-wk trial	176 patients with a comorbid anxiety disorder	8–17 yrs	Significant improvements on the ADHD Rating Scale, Pediatric Anxiety Rating Scale, Multidimensional Anxiety Scale for Children
Randomized, placebo, double-blind (Bangs et al 2005)	9 wks	142 patients with comorbid major depression	12–18 yrs	Both placebo group and atomoxetine group demonstrated improvement in depression symptoms
Double-blind, placebo, multisite (Biederman et al 2002)	9 wks	Subset of 52 girls extrapolated from sample of 291	7–13 yrs	Significant improvement noted on ADHD Rating Scale, CPRS-ADHD Index, and CGI
Double-blind, randomized, placebo (Kaplan et al 2004)	9 wks	Subset of 98 patients with comorbid ODD	7–13 yrs	Improvement in ADHD only, no improvement in ODD symptoms

Abbreviations: ADHD, attention deficit hyperactivity disorder; CAARS, Conners' Adult ADHD Rating Scale; CPRS, Conners' Parent Rating Scales; ODD, oppositional defiant disorder; CGI, clinical global impression.

ADHD Rating Scale-IV with the Clinical Global Impressions-ADHD Severity, Conners' Parent Rating Scale-Revised: Short Form used for secondary analysis. In each trial atomoxetine was found to reduce ADHD Rating Scale scores significantly more than placebo. Six patients discontinued medication owing to adverse events including irritability, chest pain, aggression, tic-like movements, and vomiting. Frequently reported adverse events included headache, abdominal pain, rhinitis, decreased appetite, and pharyngitis. Twenty-two percent of patients reported a decrease in appetite compared with 7% in the placebo group. The mean weight loss in the atomoxetine group was 0.5 kg. Very slight but statistically significant increases in diastolic blood pressure and pulse were noted (Spencer, Heiligenstein, et al 2002)

A double-blind, placebo study was completed with 170 children and adolescents, ages 6–16 years. Subjects were randomly assigned to receive placebo or atomoxetine in once-daily dosing for 6 weeks. Atomoxetine was begun at 0.5 mg/kg daily for 3 days, increased to 0.75 mg/kg daily for 4 days, and then titrated to 1.0 mg/kg daily. In those subjects who continued to demonstrate significantly elevated symptoms, the dose was increased to 1.5 mg/kg daily at 4 weeks. Two percent of patients on atomoxetine discontinued medication owing to adverse events (vomiting, somnolence). One patient in the placebo group discontinued owing to emotional lability. While 19 patients reported nausea or vomiting, this side-effect appeared to resolve over time. Other adverse events included asthenia, dizziness, headache, and rhinitis. Statistically significant improvements were noted on the ADHD Rating Scale-IV-Parent Version, Clinical Global Impressions-ADHD-Improvement Scale, and Conners Parent Rating Scale-Revised: Short Version. A daily diary was kept by parents to assess length of efficacy through the day. It should be noted the daily diary measurements have not been studied for psychometric characteristics. However, in reviewing the daily diaries, there was evidence that medication effect continued to be present later in the day, despite the short half-life, even with the once-daily dosing (Michelson et al 2002).

Michelson et al (2001) completed a 13-site double-blind placebo study of atomoxetine in patients ages 8–18 years. The medication was begun after a 12- to 18-day evaluation and a medication washout period. The 297 subjects were randomized to daily doses of 0.5 mg/kg, 1.2 mg/kg, and 1.8 mg/kg or placebo medication. Approximately 71% of the subjects were male. Medication or placebo was given in 2 divided doses over an 8-week period. Response was measured by the ADHD Rating Scale, the Conners' Parent Rating Scale-Revised: Short Form, the Clinical Global Impressions-Severity scale, Children's Depression Rating Scale-revised, and the Child Health Questionnaire. Significant improvement was noted in social and family functioning as well as the core ADHD symptoms of inattention, hyperactivity, and impulsivity at the daily doses of 1.2 mg/kg and 1.8 mg/kg. Some data supported a graded dose-response. While baseline scores on the CDRS-R were subclinical, improvement was still noted on this measure in the higher atomoxetine dose groups compared with placebo. Of interest, this study also examined response differences between rapid and slow CYP 2D6 metabolizers. Results indicated improvement in both groups, with greater improvement seen in slow metabolizers than rapid metabolizers. As these groups were small, however, statistical measurements could not be computed (Michelson et al 2001).

Once-daily dosing of atomoxetine in 197 children, ages 6–12 years was assessed in a double-blind, placebo-controlled trial over 8 weeks at 12 outpatient sites. Symptoms were assessed with the ADHD Rating Scale-IV. The mean daily dose was 1.3 mg/kg. Significant improvement was noted in the atomoxetine group which extended into evening hours as well as morning hours. Adverse events occurring more frequently in the atomoxetine treated group included decreased appetite, somnolence, and fatigue (Kelsey et al 2004).

A randomized, double-blind, placebo-controlled study was completed over 9 months in a group of children and adolescents who had responded to atomoxetine in a 12-week open study. A total of 416 patients were randomized to atomoxetine or placebo. The ADHD Rating Scale-IV, Clinical Global Impressions-Severity scale, and Child Health Questionnaire were used to assess patients at the end of 9 months. Mean dose at the end of the study was 1.56 mg/kg daily. Relapse, defined as a return to 90% of baseline symptom severity, was found in 22.3% of patients on atomoxetine compared with 37.9% of patients on placebo. In addition, patients receiving atomoxetine demonstrated superior psychosocial functioning than patients receiving placebo. Nine of 292 patients receiving atomoxetine discontinued medication because of adverse events compared with 1 of 124 patients in the placebo group. Gastroenteritis and pharyngitis were more common adverse

events in the atomoxetine group. This group also gained weight more slowly than the placebo group. No significant differences between the two groups were found on routine labs or cardiovascular measures (Michelson et al 2004).

A randomized, double-blind placebo study completed on 293 children and adolescents with ADHD for 8 weeks assessed response with the ADHD Rating Scale IV-Parent Version (investigator scored), Conners' Parent Rating Scale-Revised-Short Form, Clinical Global Impressions-ADHD-Severity Scale and the parent-rated Child Health Questionnaire. Thirty-nine percent of the patients had comorbid oppositional defiant disorder. Both groups responded significantly to atomoxetine compared with placebo at 1.8 mg/kg daily. The ADHD-only group responded significantly better to atomoxetine than placebo at 1.2 mg/kg daily but the group with ADHD and oppositional defiant disorder (ODD) did not. It was proposed that possibly children and adolescents with ADHD and ODD may require higher doses for a positive response to medication (Newcorn et al 2005).

The efficacy of once-daily atomoxetine was assessed in a randomized, placebo-controlled study of 153 children with ADHD. Atomoxetine up to 1.8 mg/kg daily was administered for 7 weeks. Teacher ratings using the ADHD Rating Scale-IV, Teacher Version were utilized based on an investigator phone interview with the teacher. The total scores as well as the inattentive and hyperactive–impulsive subscales were significantly improved in the group receiving atomoxetine. Six patients discontinued medication owing to adverse events including abdominal pain, emotional disturbance, feeling abnormal, and vomiting. No patients in the placebo group discontinued medication (Weiss et al 2005).

In a 12-week randomized trial, 176 patients ages 8–17 with ADHD and an anxiety disorder (generalized anxiety disorder, separation anxiety disorder, or social phobia disorder) were randomized to receive atomoxetine or placebo. After receiving 2 weeks of placebo medication, the atomoxetine group received 1.2 mg/kg daily of medication in twice-daily dosing. Symptoms were assessed with the ADHD Rating Scale, the Pediatric Anxiety Rating Scale, and the Multidimensional Anxiety Scale for Children. There was significant improvement in ADHD symptoms as well as significant improvement in anxiety compared with placebo. Decreased appetite was the one adverse event that occurred more commonly in the atomoxetine group (Sumner et al 2005).

One hundred forty-two patients ages 12–18 with ADHD and major depression were randomized to receive atomoxetine or placebo for 9 weeks. Most patients were male. The target atomoxetine dose was 1.2 mg/kg daily with the possibility of increase to 1.8 mg/kg daily if needed. Response to medication was measured with the ADHD-Rating Scale, Children's Depression Rating Scale and Young Mania Rating Scale. Both the atomoxetine group and the placebo group demonstrated significant improvement in depression symptoms. Two patients in each group demonstrated the appearance of mania. Nausea and decreased appetite were more common in the atomoxetine group. No suicidal ideation or behavior was noted in either group (Bangs et al 2005).

A subset of 52 girls, ages 7–13, was extrapolated from a larger sample of 291 children with ADHD, to participate in a double-blind, placebo-controlled, multisite study comparing atomoxetine with placebo over a 9-week period. One subject was unable to complete the study secondary to a personal conflict. Behaviors were measured with the ADHD Rating Scale, Conner's Parent Rating Scale-Revised ADHD Index and Clinical Global Improvement Scale – ADHD short form. A statistically significant improvement was documented for both inattention and hyperactive–impulsive behaviors. Only 1 patient discontinued from both the atomoxetine group and placebo group for side-effects. The most common side-effects were abdominal pain (29%), rhinitis (26%), and headache (26%) (Biederman et al 2002).

Another subset analysis was completed on 98 child patients from 2 sites where double-blind, randomized, placebo-controlled trials were being completed. Children with ADHD as well as ODD were identified with the Diagnostic Interview for Children and Adolescents-IV (DICA-IV), the ADHD Rating Scale-IV-Parent Version, Investigator Administered/Scored, Conners' Parent Rating Scales-Revised, short version, and the Clinical Global Impression-ADHD Severity Scale. While the patients were found to improve on ADHD ratings in this subgroup, ODD symptoms were not found to improve with atomoxetine (Kaplan et al 2004).

As noted in some of the above studies, atomoxetine has been studied in groups of children and adolescents with ADHD and the comorbid condition of Oppositional Defiant Disorder. It has been suggested that efficacy of atomoxetine in the autism spectrum population should be studied, as this population frequently presents with hyperactive–impulsive behaviors, and aggression. (Aman 2004) Other populations that would potentially benefit from further study include preschool age children with ADHD, patients with epilepsy

(Schubert 2005), and patients with sleep disturbance (Steer 2005).

Comparisons in response to atomoxetine were analyzed for children ages 6–11 (510 receiving atomoxetine, 341 receiving placebo) and adolescents ages 12–17 (107 receiving atomoxetine, 69 receiving placebo). Responses were measured with the ADHD Rating Scale, Conners' Parent Rating Scale, and Clinical Global Impressions of Severity. Adolescents were noted to have lower baseline ADHD scores. Both groups responded to treatment with atomoxetine with no statistical differences in response rates between the two groups. Children were noted to have higher rates of somnolence and headaches compared to placebo (Wilens et al 2006).

Safety

Atomoxetine has been shown to be a well-tolerated and safe medication alternative to the stimulants for the treatment of ADHD. Clinical trials to date have focused on short-term use; data on the safety of long term use are not yet available.

Side-effects

The most common side-effects include headache, abdominal pain, nausea, vomiting, decreased appetite, weight loss, irritability, insomnia, and sedation. In adults, there have been reports of urinary retention, erectile dysfunction, dysmenorrhea, and decreased libido (Michelson et al 2003). Less common but significant side-effects that have been reported include elevated liver enzymes (Eli Lilly and Company 2004 December 21, pers comm), and motor tics (Lee et al 2004; Ledbetter 2005). However, an 18-week, double-blind, randomized, placebo trial was completed with 148 patients with ADHD and a comorbid tic disorder ages 7–17. Tics were measured with the Yale Global Tic Severity Scale. Atomoxetine did not exacerbate tics and there was a trend for improvement of tics in the atomoxetine group compared with the placebo group (Allen et al 2005). There are several reports regarding induction of mania (Steinberg et al 1985; Henderson 2004; Henderson and Hartman 2004) and a report of an allergic reaction with angioneurotic edema and urticaria (Spencer et al 1998). A study reviewing cardiovascular measurements indicated an increase in mean change for heart rate and blood pressure but no changes in the QTc interval. Effects on blood pressure and heart rate remained during atomoxetine treatment, resolving with discontinuation of the medication (Wernicke et al 2003). In adult trials there has been an increased rate of urinary retention or hesitation compared with the placebo group. (Eli Lilly 2003) Thus, complaints of urinary retention or hesitation may be related to the use of atomoxetine.

More recent concerns have focused on more serious side-effects. There have been 2 reports of elevated liver enzymes in patients taking atomoxetine. The enzymes normalized in both patients after the atomoxetine was discontinued. In one patient elevated liver enzymes and jaundice recurred when the medication was resumed. The current recommendation is to monitor for fatigue, jaundice, right upper quadrant tenderness, dark urine, and unexplained flu-like symptoms. Regular monitoring of liver enzymes is not recommended at this time (Eli Lilly and Company 2004 December 21, pers comm).

More controversial is the recent report of an increased risk of suicidality associated with the medication that has resulted in the addition of a black box warning by the FDA. Comments in the black box warning include the following: "Strattera (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with ADHD. Anyone considering the use of Strattera in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber." (Eli Lilly and Company 2005 November 4, pers comm). An independent review of reports from the Eli Lilly trials completed by Greenhill summarized the following data that prompted the decision: 5 children out of the 1357 receiving atomoxetine developed suicidal ideation (0.37%) with 2 cases considered to have clinically important levels of suicidal ideation. One child out of the 1357 was reported to have attempted to harm himself (0.00074%). This risk was statistically significant in comparison to the 0 incidence of suicidal ideation/attempts in the 851 patients who received placebo. Of the patients reported to have had suicidal ideation or behavior, all were between the ages of 7 and 12 years. In contrast, no adolescents were reported to have experienced suicidal ideation. Limited information regarding the prevalence of suicidal ideation in the general population or the ADHD population in this age group prevents accurate analysis of the actual risk associated with medication use. A recommendation was made for the FDA to conduct further trials as well as to create an independent panel of experts to review data on this issue. In addition, the importance of a comprehensive treatment plan in

conjunction with medication management has been stressed (Sarles 2005).

The concerns regarding suicidal ideation raise an interesting and important issue regarding the classification, analysis, and understanding of the pharmacodynamics of atomoxetine. Atomoxetine is currently classified as a nonstimulant medication for ADHD. The potential side-effect of agitation, along with what is known about the neurophysiological response, however, is similar to effects observed in stimulant medications. Indeed, the definition of a stimulant from Stedman's Medical Dictionary is as follows: "1. Stimulating; exciting to action. 2. An agent that arouses organic activity, strengthens the action of the heart, increases vitality, and promotes a sense of well-being; classified according to the parts upon which they chiefly act: cardiac, respiratory, gastric, hepatic, cerebral, spinal, vascular, genital." Also, emerging research regarding effect on brain physiology finds similar effects between stimulants and atomoxetine (Gilbert et al 2005).

In contrast, atomoxetine, which was initially developed for the treatment of depression, shares common characteristics with norepinephrine reuptake inhibitor antidepressants. It is interesting to note that concerns have also been expressed about suicidal ideation and behavior related to antidepressants. The link between suicidal behaviors and antidepressant use remains unclear at this time, as many confounding issues challenge attempts to understand this question critically. Psychiatric illnesses, especially mood disorders, are known to increase the risk of suicidal ideation and suicide attempts. The retrospective data analysis on suicide has limitations in that the original data lacked pretreatment information about suicidal behaviors and sometimes contained limited information regarding suicidality (Cheung et al 2006). Proposed mechanisms of action for the increase in suicidal ideation with antidepressants includes akasthesia, anxiety, and restlessness as well as the increase in energy secondary to treating the underlying disorder of depression. The relationship between suicidal ideation and medications including antidepressants and atomoxetine remain unclear.

In summary, atomoxetine shares characteristics with both stimulant medications and antidepressants, while currently being classified as a "nonstimulant". It is possible a similar mechanism of action is responsible for the risk of suicidal ideation, behavior, and agitation. Further research is clearly needed in this area.

Potential for abuse has been assessed in subjects with a history of substance abuse. There has been no report of pleasurable effects from taking atomoxetine which implies a limited abuse potential for this medication (Heil et al 2002).

Consideration should be given for dosing in special populations. Patients with impaired hepatic function will require a decrease in dosing. Significant reductions in clearance of atomoxetine were observed in 10 adult patients with hepatic impairment compared with 10 adult controls. The degree of impairment correlated with reduction in clearance of atomoxetine. The target dose should be reduced by 25% in patients with moderate hepatic insufficiency to 50% in patients with severe hepatic insufficiency (Chalon et al 2003; Eli Lilly 2003). Patients with renal insufficiency do not require alterations of dosing regimen (Eli Lilly 2003). Atomoxetine should be used with caution in patients with significant cardiovascular disease as it has been documented to increase blood pressure and pulse (Wernicke et al 2003).

Overdose

There is at least 1 report of significant complications from atomoxetine overdose. A 15-year-old male patient took 1200 mg (22 mg/kg) of atomoxetine about 1½ hours before coming to the emergency room. The patient experienced a generalized seizure with postictal confusion about 3 hours after ingestion with a second generalized seizure 2 hours later. In addition he demonstrated tachycardia with a prolonged QTc interval of 607 msec 3 hours after ingestion and 435 msec 6 hours after ingestion. There did not appear to be additional medications included in the overdose. The patient's symptoms resolved and he was discharged to a psychiatric inpatient facility 2 days after the event (Sawant and Daviss 2004). Atomoxetine ingestions were reviewed from the records of 3 regional poison control centers. Forty patients with follow up data were identified who had taken atomoxetine alone. Symptoms reported included tachycardia, drowsiness, nausea, hypertension, and vomiting. One child was reported to have had a seizure. The only arrhythmia reported was sinus tachycardia. The report concluded that activated charcoal and/or observation were appropriate in the management of atomoxetine overdose. No clinically significant cardiovascular problems requiring intervention occurred (Spiller et al 2005).

Drug interactions

Because atomoxetine is metabolized through the CYP2D6 system, interactions can occur with medications that are inhibitors of this system such as paroxetine, fluoxetine, and quinidine. Other 2D6 inhibitors include citalopram,

escitalopram, bupropion, sertraline, chlorpromazine, hydroxyzine, and clomipramine. Twenty-two healthy subjects with rapid metabolism of the 2D6 system were administered 20 mg of atomoxetine to steady state. Twenty mg of paroxetine was added for 17 days with coadministration with atomoxetine for the last 6 days. Paroxetine increased the maximum concentration of atomoxetine by 3.5-fold and half-life of atomoxetine by 2.5-fold. There was no change in paroxetine level with the addition of atomoxetine (Belle et al 2002). It is recommended to begin treatment at standard doses but pursue further dose increases with caution. Inducers of this system include dexamethasone and rifampin. No studies were found that examine the interaction between atomoxetine and 2D6 inducers. Atomoxetine has not been shown to have an effect on the metabolism of other medications metabolized through 2D6.

Administration of atomoxetine with albuterol may increase heart rate and/or blood pressure. Administration with a monoamine oxidase inhibitor (or within 2 weeks of administration of this agent) is contraindicated because of the risk of a hypertensive crisis (Eli Lilly 2003).

Administration with methylphenidate does not appear to increase the risk of cardiovascular problems more than can occur with methylphenidate alone, but there is limited research on this combination. A case report reviewed 4 cases in which patients received a combination of atomoxetine with a stimulant medication (3 patients on a mixed amphetamine salt and 1 patient on OROS methylphenidate). In 2 cases the atomoxetine was added to the stimulant medication when the patient had difficulty with complete coverage of ADHD symptoms throughout the day. In the other 2 cases a stimulant medication was added to atomoxetine when a partial benefit was observed at a maximum dose of atomoxetine. In all 4 cases, improvement in functioning was reported with no evidence of significant adverse events (Brown 2004).

A randomized, double-blind, placebo study was conducted on 173 patients ages 7–17 with ADHD and concomitant anxiety or depression. Patients received fluoxetine or placebo for 8 weeks in conjunction with atomoxetine the last 5 weeks. Reductions in ADHD, depressive symptoms, and anxiety symptoms were marked in both treatment groups. Overall, the combination of fluoxetine and atomoxetine was well tolerated, although this group had greater increases in blood pressure and pulse compared with the atomoxetine-only group (Kratochvil et al 2005).

Dosage–administration

Atomoxetine is given at a target dose of 1.4 mg/kg daily and can be given in a single daily dose or in twice-a-day dosing. It is recommended to begin at 0.5 mg/kg for 4 days before titrating up to the target dose. Medication effect may take up to 4 weeks to occur. Patients should be monitored for medication effect via rating scales completed initially at 4 weeks. Weight, height (for growing children and adolescents), blood pressure, and pulse should be monitored at every visit. Liver function tests are indicated if there is report of fatigue, jaundice, right upper quadrant pain, or flu-like illness. If the patient has pre-existing hypertension, tachycardia, or cardiovascular disease additional caution is advised, as atomoxetine has not been studied in patients with these conditions and the medication is known to slightly increase blood pressure and pulse.

The medication should not be administered in conjunction with a monoamine oxidase inhibitor. While there are no specific recommendations when atomoxetine is given with albuterol or stimulant medication, careful monitoring of cardiovascular function is recommended. Because of concerns about mydriasis, atomoxetine is contraindicated in patients with narrow-angle glaucoma. There have been no controlled studies on the use of atomoxetine in pregnancy. Atomoxetine is currently a category C medication for use in pregnancy.

In a randomized, double-blind, placebo-controlled trial of 288 children with ADHD, morning vs evening dosing of atomoxetine for 6 weeks was evaluated. Children with ADHD were assessed with the ADHD Rating Scale and the Clinical Global Impression-Severity Scale. Both groups responded significantly better than those on placebo. However, the group receiving a morning dose did better than the group receiving an evening dose on the hyperactive–impulsive subscale of the ADHD-RS, and the CGI-Severity Scale. At this time, the importance of timing of dose, if any, is not clear. In contrast, a second study that analyzed response to morning vs evening dosing of atomoxetine, found the evening dose was reported as better tolerated. Both groups demonstrated a positive response to medication (Kelsey et al 2005).

While plasma levels of atomoxetine are not currently used to direct dosing, a recent study found a correlation between atomoxetine level and response to medication. Patients with plasma levels greater than 800 ng/mL showed a greater, although not a statistically significant,

improvement in ADHD symptoms. It was noted that in 1 patient, this required a daily dose of 2.4 mg/kg (Dunn et al 2005).

In a prospective, placebo-controlled trial of atomoxetine in children and adults, patients were monitored for changes in symptoms and adverse events after discontinuation of atomoxetine. There was no evidence of a discontinuation syndrome. Symptoms of ADHD were noted to worsen but not return to pretreatment levels of severity (Wernicke et al 2004).

Conclusion

Atomoxetine is a novel compound that has clinical utility both for children and adults with ADHD. It is unclear at this time whether atomoxetine is also effective in the treatment of anxiety or depression. Data are also mixed as to whether children with comorbid ODD demonstrate improvement of oppositional behaviors secondary to a medication trial. Further research is needed on efficacy of atomoxetine in special populations with attentional problems such as patients with epilepsy or autism spectrum disorders. Benefits specific to atomoxetine include the once-daily dosing, sustained medication effect, and lack of risk for abuse. It is generally well tolerated, with the most common side-effects including appetite suppression, mild weight loss, and nausea. Serious but rare potential side-effects may include agitation, irritability, elevated liver enzymes, rash, tics, and suicidal ideation. Further research into the pharmacodynamics and safety of the medication is indicated. Additional data on the safety of long term use are not currently available. Atomoxetine is a useful addition to nonstimulant treatment options for patients with ADHD who have not responded to stimulant medication or are unable to tolerate problematic side-effects. Atomoxetine should also be considered an alternative in patients with ADHD and a history of substance abuse.

Disclosures

The author has no conflicts of interest to disclose.

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