

Atomoxetine for the treatment of attention-deficit/hyperactivity disorder in children and adolescents: a review

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Objective: This review examines and summarizes the pharmacodynamic and pharmacokinetic properties, short- and longer-term efficacy, the moderating effect of comorbid disorders, as well as short- and long-term safety and tolerability of atomoxetine for the treatment of pediatric attention-deficit/hyperactivity disorder (ADHD).

Methods: A systematic literature search was performed to review the extant literature on articles pertaining to the pharmacological treatment with atomoxetine in pediatric and/or adolescent ADHD.

Results: There is an extensive literature on atomoxetine; over 4000 children have participated in clinical trials of atomoxetine, demonstrating its short- and longer-term efficacy. In addition, studies have examined the moderating effect of comorbid disorders on atomoxetine response, as well as atomoxetine's therapeutic potential for other psychiatric conditions. Short- and longer-term safety and tolerability continue to be reported.

Conclusions: Atomoxetine is indicated for both acute *and* maintenance/extended treatment of pediatric ADHD. Clinicians and families must be familiar with atomoxetine's evidence base, including its profile of clinical response and its possible effectiveness in the presence of comorbidity.

Keywords: ADHD, atomoxetine, pediatric

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common childhood neurobehavioral disorder in the United States with an estimated prevalence of 6% to 8%.¹ Both the American Academy of Pediatrics (AAP) and the American Academy of Child and Adolescent Psychiatry (AACAP) recommend either a stimulant or atomoxetine as psychopharmacological agents for its treatment.^{2,3} Atomoxetine (Strattera®; Eli Lilly and Company), a selective norepinephrine reuptake inhibitor (SNRI), is the only non-stimulant approved by the FDA for the treatment of ADHD in children, adolescents and adults. While stimulant class medications are frequently used as first-line agents, atomoxetine may also be considered as an initial choice, particularly in the presence of select comorbid disorders, including active substance abuse, anxiety disorder or tic disorder.²

Here we aim to summarize the extensive literature on atomoxetine, including its pharmacodynamic and pharmacokinetic properties, short- and longer-term efficacy, the moderating effect of comorbid disorders, as well as short- and long-term safety and tolerability. We will close with summary clinical recommendations for the use of atomoxetine in pediatric ADHD.

Pharmacodynamics

Atomoxetine is a potent norepinephrine (NE) uptake inhibitor in vitro and in vivo with relatively low affinity for 5-HT and DA uptake sites;^{4,5} it has 290-fold lower

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affinity for dopamine transporters than norepinephrine.⁶ Mechanistically, inhibition of the NE transporter blocks synaptic clearance of NE, thereby increasing synaptic NE concentrations in noradrenergic pathways. For example, NE in prefrontal cortical (PFC) regions has been shown to play a key role in attention and higher cognitive processes.⁶

In animal studies, atomoxetine has been shown to selectively increase dopamine (DA) to a similar magnitude as NE in the PFC, due to region-specific shared monoamine uptake inhibition, while not altering DA in other dopamine-rich brain regions such as nucleus accumbens and striatum.⁶ In addition, atomoxetine robustly increased NE in other brain regions with a substantial density of norepinephrine transporters; atomoxetine rapidly and persistently increased norepinephrine in rat occipital cortex, lateral hypothalamus, dorsal hippocampus, and cerebellum.⁷

Pharmacokinetics

Absorption and distribution

Atomoxetine is efficiently absorbed after oral administration (range 63%–94%); its bioavailability is minimally affected by food. After oral administration, atomoxetine reaches a maximum plasma concentration in approximately 1 to 2 hours. Atomoxetine is highly protein bound, roughly 98%, specifically to albumin.^{8–10}

Metabolism and elimination

There are three metabolic pathways involved in the clearance of atomoxetine; aromatic ring-hydroxylation, benzylic hydroxylation, and N-demethylation. The hepatic enzyme cytochrome P450 2D6 (CYP2D6) is the primary metabolic pathway for atomoxetine, yielding its primary oxidative metabolite 4-hydroxyatomoxetine.^{9,11} Over 80% of the atomoxetine dose is excreted primarily as 4-hydroxyatomoxetine-O-glucuronide in the urine, with a minority excreted in the feces.¹² It is well known that there are distinct differences within populations of CYP2D6 activity (extensive versus poor metabolizers), and that genetic tests are presently available to identify this variability. Those persons who are deemed “poor metabolizers” (PM) of CYP2D6 drugs (about 7% of the Caucasian population) have been shown to have mean peak atomoxetine concentrations up to 5-fold higher and total plasma exposure of atomoxetine 10-fold higher than persons who have extensive (normal) metabolic (EM) activity.¹³ Atomoxetine has a plasma half-life of about 5.2 hours in extensive metabolizers,^{9,12} compared to 22 hours in poor metabolizers, as atomoxetine is metabolized through several alternative CYP pathways.¹³ From a clinical

standpoint, the important question is: what is the practical impact of CYP metabolism status on the treatment of a given patient? A recent pooled analysis addressed this question by examining the relationship between CYP2D6 status and clinical response in children and adolescents with ADHD.¹³ Efficacy data were derived from 6 acute clinical trials (N = 559 EMs, 30 PMs), while safety and tolerability data was assessed using a pooled database from 14 studies (N = 3017 EMs, 237 PMs). Efficacy analyses demonstrated significantly greater improvements in ADHD rating scale scores and rates of response in PMs as compared to EMs (80% and 59% response rates in PMs and EMs respectively). However, the pooled efficacy and PK data found a low (0.179) correlation coefficient between response and peak concentration; the differential efficacy between EMs and PMs may instead be related to total plasma atomoxetine exposure or area under the curve (AUC).¹³ In this same analysis, reduced appetite, insomnia and tremor were seen in significantly greater rates in PMs, compared to EMs.¹³ In addition, significantly greater increases in mean pulse rate at endpoint (+3.9 bpm) and in mean diastolic blood pressure (DBP) at endpoint (+1.6 mmHg) were observed in PMs, as compared to EMs.¹³ The authors suggest that these differences may be due to increased noradrenergic tone in PM and/or due to persistent effects due to more constant drug concentrations throughout the day.

Since atomoxetine is highly protein bound, systemic clearance of atomoxetine may be significantly reduced in those patients with hepatic impairment. Dosage adjustment is recommended in these patients.¹⁴

Efficacy

Short-term atomoxetine treatment in children and adolescents

Pivotal studies of atomoxetine in pediatric ADHD first emerged in 2001. Following a small open-label dose ranging study,¹⁵ a large randomized controlled trial demonstrated superior efficacy of 1.2 mg/kg/day and 1.8 mg/kg/day doses compared with placebo.¹⁶ This multicenter 8-week trial included 297 children and adolescents with ADHD. All subjects began with 0.5 mg/kg/day, in divided (twice daily) dosing, increased at weekly intervals. Efficacy was measured using parent and investigator ADHD rating scales; the 1.2 mg/kg and 1.8 mg/kg doses were significantly superior to placebo at reducing ADHD symptoms, with similar improvement for inattentive and hyperactive/impulsive subtype symptoms. Improvements in social and family functioning were also observed using a number of secondary outcome measures.

The magnitude of improvement with atomoxetine treatment as judged by teachers has been found to be similar (effect size = 0.63) to that seen in studies based on investigator interviews with parents (0.6 and 0.8).¹⁷ This study, by Weiss et al¹⁷ used the ADHD-RS-IV-Teacher:Inv as the primary outcome measure. This scale was completed by investigators during a 4-day period before each study visit, based on a telephone interview with the child's primary teacher. Teachers reported improvement within 1 week of initiating therapy.

Overall, short-term ADHD symptom improvement has been demonstrated in multiple settings as assessed by clinician, parent, and teachers, and as measured according to a variety of outcomes over the short term. A recent meta-analysis reported the number-needed-to-treat (NNT) for atomoxetine treatment response (reduction of $\geq 25\%$ in ADHD-RS total score from baseline) was 3.43 (95% CI, 2.79–4.45).¹⁸ Significant improvement compared with those treated with placebo has been demonstrated across efficacy measures, in younger (6–7 years) and older (8–12 years) children: ADHD-RS total score: younger ES = 0.77, older ES = 0.65; Inattentive subscale: younger ES = 0.71, older ES = 0.59; Hyperactive/Impulsive subscale: younger ES = 0.76, older ES = 0.62; CGI-ADHD-S score: younger ES = 0.62, older ES = 0.59.¹⁹ However, overall in the treatment of pediatric ADHD, superior effect sizes are consistently observed with immediate-release and long-acting stimulants, as compared to non-stimulants, including atomoxetine.²⁰

When does clinical response occur?

The full efficacy of atomoxetine may not be seen in short-term treatment studies. In two very short-term (3-week) open-label studies with OROS methylphenidate²¹ and mixed amphetamine salts extended release (MAS XR) comparators,²² each stimulant medication demonstrated superior effectiveness over atomoxetine, while a 10-week study by Kratochvil et al²³ reported similar effectiveness with either atomoxetine or immediate-release methylphenidate. A gradual clinical response to atomoxetine is depicted in the report by Wilens et al; in a large sample (N = 882) of adolescents, mean ADHD-RS score continued to decline up until the 3rd month of treatment, at which point scores stabilized and remained so, over 24 months of treatment.²⁴ Thus, patience with this medication may be necessary in order to appreciate its full efficacy.

Does dosing matter?

In theory, twice daily dosing may provide greater efficacy with more consistent plasma atomoxetine exposure, consistent

with PK findings.¹³ However, several trials have demonstrated that atomoxetine appears to be as effective when the dose is given as a single daily dose.^{17,25,26} In the latter study,²⁶ which used a more rapid early dose titration schedule, statistically significant improvement was observed after 1 week of treatment, with evidence for superior efficacy, compared with placebo, as soon as the first day of treatment, according to daily analyses of parent ratings.

For example, Kelsey et al²⁶ reported on a large group of children receiving 8 weeks of once daily atomoxetine or placebo. Atomoxetine titration was relatively rapid, beginning at 0.8 mg/kg/day for 3 days, increasing to 1.2 mg/kg/day for 4 weeks, with the option to increase to 1.8 mg/kg/day according to tolerability and clinical assessment. Using a novel instrument, parents rated children's behaviors in the morning (before AM dosing and representing trough levels) and evening (after 6 PM), such as getting up, doing homework, and sitting through dinner. Parents recorded observations using an electronic entry system to record on a daily diary. Total score, as well as evening and morning subscales showed statistically significant improvements from baseline to endpoint. Comparisons of mean changes in individual parent ratings demonstrated significant atomoxetine-specific reductions for 5 of 8 evening items and 2 of the 3 morning items. Results obtained with a validated scale assessing evening behaviors (Conners' GIPE) also showed statistically significant improvements in total score for evening behaviors from baseline to endpoint. The treatment effect size in this study for the primary outcome measure was 0.7, compared with 0.8, 0.7, and 0.6 in the studies of twice-daily atomoxetine.²⁶

What about atomoxetine response in children previously treated with stimulants?

In a unique crossover design, Newcorn et al²⁷ reported on the response to atomoxetine in children who had been previously treated with stimulant medication. Youth with ADHD, any subtype, were randomly assigned to receive 0.8 to 1.8 mg/kg/day of atomoxetine (N = 222), 18 to 54 mg/day of OROS MPH (N = 220), or placebo (N = 74) for 6 weeks. For youth with a history of stimulant treatment (N = 301), the response rate for atomoxetine was 37%, as compared to the 57% response rate observed in patients who were stimulant naive at study entry (N = 191). Meta-analysis demonstrating the short-term efficacy of atomoxetine in children and adolescents includes high rates of children (57%) and adolescents (75%) with prior stimulant exposure.²⁴

Special populations: children with poor prior stimulant response

The Newcorn et al²⁷ trial is the only large, controlled study to offer within-subject data (crossover) characterizing treatment response to atomoxetine in children who did not respond to stimulant treatment during the study itself ($\geq 40\%$ decrease in ADHD rating scale). After 6 weeks of initial treatment, under double blinded conditions, children treated with OROS MPH were switched to atomoxetine. For the 70 youths who did not respond to OROS MPH in the trial, 43% subsequently responded to atomoxetine.

Overall, despite limitations noted by the authors (eg, no washout period between the two treatments), there are helpful clinical findings in this novel study. About one-half of subjects who switched to atomoxetine after completing 6 weeks of methylphenidate responded robustly to both treatments. Yet, the majority of the others responded preferentially to one treatment, either methylphenidate or atomoxetine. A sizeable smaller number (22%) were non-responders to both methylphenidate and atomoxetine. Differential response may be due to pharmacologic, metabolic and pharmacokinetic differences at an individual level.

There are two previous studies in which children were a priori selected for atomoxetine treatment based upon incomplete response or intolerance to prior stimulant treatment.^{28,29} In the Quintana et al²⁸ study, significant mean reductions in ADHD-RS Parent:Inv total scores were observed from baseline to end point (32.1 vs 22.6; $p < 0.001$). However, this study was limited by a stepwise cross titration, with ongoing stimulant treatment during the first 2 weeks of atomoxetine treatment.

Hammerness et al²⁹ conducted a prospective short-term, open-label study of atomoxetine in the treatment of youth with ADHD who had been non-responsive and/or had a history of poor stimulant tolerability. In this study, atomoxetine monotherapy (doses of up to 1.4 mg/kg/day) was associated with significant reductions in ADHD symptomatology and significant overall global improvement (CGI-I ADHD). The magnitude of response to atomoxetine (53% with 30% reduction in ADHD-RS; 41% with 50% reduction) was consistent with previous controlled clinical trials of atomoxetine in pediatric ADHD.¹⁶

Special populations: young children

Kratochivil et al³⁰ recently reported on the safety and effectiveness of atomoxetine in an open-label study with 22 subjects, ages 5 to 6. The mean final dose was 1.25 mg/kg/day. Comparable efficacy to older age groups was observed, with

a mean decrease of 21 ADHD-IV RS total points (SD = 12.8, $p < 0.001$). Similar mean decreases of 10 points (SD = 7.48, $p < 0.001$) on the inattentive subscale, and 11 points (SD = 7.04, $p < 0.001$) on the hyperactive/impulsive subscale were reported.

Can atomoxetine be combined with stimulants?

Due to the presence of residual ADHD symptoms following primary treatment, adverse effects or psychiatric comorbidity, clinicians commonly utilize a combination of medications for youth with ADHD.³¹ Two recent studies examined the combination treatment of atomoxetine and stimulant.^{32,33} Carlson et al³² took a small group of children who did not initially respond to 4 weeks of atomoxetine and randomized them to atomoxetine + OROS MPH (N = 9) or atomoxetine + placebo (N = 12) for an additional 6 weeks. There were no significant differences between groups; however the small sample size and the use of subjects who were resistant to previous stimulant trials and retested on MPH limits the finding.

Wilens et al³³ conducted a similar design, 2-phase, 7-week open study in children aged 6 to 17 years. However, children were not selected based upon prior lack of response to stimulant treatment. After monotherapy with atomoxetine for 4 weeks, partial responders to atomoxetine added OROS MPH (titrated to 54 mg over a subsequent 3 weeks) to their regimen. Subjects were assessed on multiple outcomes including ADHD, executive functioning and adverse effects. Of fifty subjects treated with the combination therapy, 41 subjects completed the entire protocol. There was a 40% reduction in their ADHD-RS from the beginning of combination treatment through the end of study (from 21.14 ± 9.9 to 12.8 ± 9.7 , $t = 6.5$, $p < 0.0001$). In addition, there was a clinically significant reduction in the Clinical Global Index of ADHD severity from moderate to mild ADHD as well as improvements in executive functioning.³³ Hammerness et al²⁹ reported the tolerability of this combined regimen; compared to atomoxetine alone, adjunct OROS MPH was associated with significantly greater rates of insomnia, irritability, and loss of appetite.

Longer-term atomoxetine: is efficacy maintained?

The benefit of maintaining pediatric patients (ages 6–15 years) with ADHD on atomoxetine has been demonstrated in controlled studies, allowing for atomoxetine to receive the unique indication for both acute and maintenance/extended treatment

of ADHD. However, according to current prescribing information, the long-term usefulness of atomoxetine for an individual patient should periodically be re-evaluated over extended treatment periods (Lilly, Product Information, Sept 2008).

In recent meta-analyses of controlled and open-label studies, the maintenance of efficacy (according to ADHD-RS-IV-Parent:Inv) is demonstrated over 2 years; 25.7% of children,³⁴ and 16.5% of adolescents discontinued due to lack of effectiveness over the study period.²⁴ Similarly, in the Spencer et al³⁵ report documenting safety of 5-year maintenance, only 16% discontinued due to lack of efficacy.

Atomoxetine maintenance has also been studied in children and adolescents in a naturalistic setting. A recent observational open-label study of patients (N = 627; mean age = 11 years) with ADHD involved children treated at 60 physicians' offices across the United States and Puerto Rico.³⁶ Physicians were prescribed atomoxetine either as initial treatment or after trying another ADHD treatment (eg, stimulants, antidepressants). Atomoxetine administration, dosing, and timing of follow-up visits occurred at each physician's discretion. Treatment length ranged from 0 to 89 weeks with an average span of 21.2 weeks. The primary measure of efficacy was the Physician Global Impression: ADHD Severity (PGI-ADHD-S) scale, which had a mean severity decrease of 0.91 (95% CI: -1.00 to -0.82, $p < 0.001$). Fifty-nine to 69% of subjects demonstrated consistent control of ADHD symptoms throughout the day, with improvement in subjects' grades reported by teachers, and improvement in subjects' behavior reported by parents.

Is there evidence of relapse after atomoxetine is stopped?

A unique study by Michelson et al³⁷ examined relapse in a large pediatric sample derived from 33 academic investigative centers in Europe, Israel, South Africa, and Australia. The study included children and adolescents who had previously participated in a 12-week open-label atomoxetine treatment.³⁸ Of the original 416 subjects, 163 (26%) completed 1 year of treatment with atomoxetine and were re-randomized to 6 additional months of treatment with atomoxetine (n = 81) or placebo (n = 82). Subject worsening of symptoms (defined as symptom severity returning to 50% of baseline) was significantly greater in those switched to placebo (47.6%), than those who remained on atomoxetine (28.4%). Buitelaar et al's³⁹ report extends these results; after 1 year, 42% of those in the placebo group would be classified as relapsers (increase in ADHD-RS total score to ≥ 1.5 standard deviations above

norm) compared with 22% of atomoxetine-treated subjects ($p = 0.010$).

Efficacy – comorbid conditions

Up to 60% of children with ADHD suffer from psychiatric comorbidity, including oppositional defiant disorder (ODD), anxiety and mood disorders, tic disorders, and pervasive development disorder (PDD).

Oppositional defiant disorder

The most common co-morbid condition of ADHD is ODD, which occurs in 40% to 60% of children with ADHD.⁴⁰ However, the methodology and patient population selected to study atomoxetine response in ODD has varied considerably. The recent meta-analysis on this topic⁴⁰ identifies some of these limitations; differences in inclusion criteria eg, subject ages (inclusion or exclusion of adolescents), study duration (6, 7, or 8 weeks of exposure), diagnostic entry criteria (1.0 vs 1.5 standard deviations above the norm).

Does atomoxetine work in children with ADHD and ODD/ODD symptoms?

In a recent report, Biederman et al⁴⁰ examined whether comorbid ODD impacted response to atomoxetine in children with ADHD. Acute-phase data were analyzed from three randomized, double-blind, placebo-controlled studies in children aged 6 to 16 with ADHD conducted in the USA and Canada.^{17,25,26} Subjects received placebo or atomoxetine (max 1.8 mg/kg/day) for 6 to 8 weeks. In this large sample, 158/512 were diagnosed with comorbid ODD. Relative to placebo, atomoxetine treatment significantly reduced ADHD symptoms in both ODD-comorbid and non-comorbid subjects, indicating that the presence of comorbid ODD did not affect ADHD treatment response. ADHD subjects also showed significant improvements from baseline on most of the psychosocial measures of the child health questionnaire regardless of the comorbidity with ODD.

Other reports have found greater efficacy in treating comorbid ADHD + ODD at higher dosing; in the Newcorn et al⁴¹ study, the comorbid group showed improvement compared with placebo at 1.8 mg/kg/day but not 1.2 mg/kg/day. However, Newcorn et al's⁴¹ findings have not been found by others.⁴⁰

In one longer-term study, Hazell et al⁴² examined the influence of comorbid ODD on the relative risk (RR) of relapse during 9 months of treatment with atomoxetine for ADHD; fewer youth with comorbid ODD relapsed during maintenance atomoxetine treatment, as compared

to youth without comorbid ODD (17% vs 26%; RR 0.67, 95% CI 0.42–1.06).

Is atomoxetine effective in reducing ODD symptoms?

In examinations of data from positive randomized clinical trials of atomoxetine in pediatric ADHD,⁴³ investigators have not observed significant decreases in ODD rating scale scores in atomoxetine treated children compared to placebo; CPRS-R:S Oppositional subscore.⁴⁴ Consistent with this analysis, Biederman et al⁴⁰ found no significant treatment difference in the CPRS-R:S oppositional subscale change scores; reduction in ODD symptoms was highly related to the magnitude of ADHD response. One study which demonstrated statistically significant improvement in ODD may have benefited from twice-daily dosing, allowing for better control of oppositional symptoms during the evening hours.⁴¹ A recent placebo controlled trial of ADHD and ODD found significant improvement for ADHD symptoms but not for ODD symptoms at endpoint analysis.⁴⁵ In this study, the investigator-rated Swanson, Nolan, and Pelham Rating Scale-Revised (SNAP-R) was used to determine treatment effect on ODD and ADHD symptoms.

Pervasive developmental disorders

Several small, short-term studies have examined the efficacy and tolerability of atomoxetine in children with PDD and ADHD symptoms. One trial with a crossover design examined atomoxetine and placebo response during 6 week periods, separated by a one week washout.⁴⁶ Twelve boys and 4 girls (7 with autistic disorder, 1 Asperger's, 8 pervasive developmental disorder not otherwise specified) all completed at least 3 weeks of each treatment condition. On the primary outcome, the Hyperactivity subscale of the Aberrant Behavior Checklist, atomoxetine was superior to placebo ($p = 0.043$, effect size $d = 0.90$). In this study, atomoxetine demonstrated significant efficacy in reducing core DSM-IV ADHD hyperactive/impulsive symptoms ($p = 0.005$, $d = 1.27$), but not inattentive symptoms ($p = 0.053$, $d = 0.89$). While atomoxetine was generally well tolerated, with no tendency to stereotypy, one participant was re-hospitalized for recurrent violence on atomoxetine. Similar effectiveness in aberrant behavior (hyperactivity subscale only) has been observed in a longer (10 week) trial, although still based upon an open trial with a small sample.⁴⁷ Improvements have also been reported in irritability, social withdrawal, stereotypy, and repetitive speech.⁴⁸

Tolerability may be an area to watch in this patient population; in one study, 5 patients (42%) discontinued because of

side effects, including gastrointestinal symptoms, irritability, sleep problems, and fatigue.⁴⁷ Although again, conclusions based on these findings cannot be made due to the very small sample size.

Tic disorders

Given that stimulant medications have been associated with the onset or exacerbation of a tic disorder, atomoxetine may offer unique efficacy and/or tolerability in children with ADHD and comorbid tic disorders; Tourette's syndrome (TS), and/or simple motor tic disorder. In the largest study to date, Allen et al⁴⁹ examined children (7–17 years) with ADHD and concurrent TS or chronic motor tic disorder in a double-blind randomized treatment study with placebo ($n = 72$) or atomoxetine (0.5–1.5 mg/kg/day, $n = 76$) for up to 18 weeks. Atomoxetine was associated with a greater reduction of tic severity at endpoint relative to placebo on the Clinical Global Impressions (CGI) tic/neurologic severity scale score (-0.7 ± 1.2 vs -0.1 ± 1.0 , $p = 0.002$); however significance was not reached in Yale Global Tic Severity Scale (YGTSS) total score, nor the Tic Symptom Self-Report total score. In a subset of this study that included only children with comorbid TS, atomoxetine was associated with significant reduction of tic severity on two of three measures.³⁵

Childhood anxiety disorders

In addition to comorbid ODD and tics, approximately one third of children with ADHD have comorbid anxiety disorders. The one large controlled study of ADHD and comorbid anxiety was published this past year. In this trial, Geller et al⁵⁰ enrolled 176 children (ages 8–17 years) who met DSM-IV criteria for ADHD and generalized anxiety disorder, separation anxiety disorder, and/or social phobia. Children were randomized to 12 weeks of atomoxetine ($n = 87$) or placebo ($n = 89$). Sixty-six patients in each group completed the study. Mean ADHD-RS-IV-Parent: Inv total score improved significantly for atomoxetine ($n = 55$; -10.5 , SD 10.6) relative to placebo ($n = 58$; -1.4 , SD 8.3; $p < 0.001$; ES = 0.84). Mean Pediatric Anxiety Rating Scale (PARS) total score also improved significantly for atomoxetine ($n = 55$; -5.5 , SD 4.8) relative to placebo ($n = 58$; -3.2 , SD 5.0; $p = 0.011$). There was also a significant reduction in independently assessed anxiety symptoms using both clinician-rated and self-rated measures.

In comparison, a study by Abikoff et al⁵¹ involved the sequential treatment of children with ADHD and anxiety using fluvoxamine. While children with ADHD and anxiety

were found to have a response rate to stimulants for ADHD that is comparable with that of children with general ADHD, subsequent blinded assignment to 8 weeks of fluvoxamine treatment was not found to be statistically superior to placebo, based on the Pediatric Anxiety Rating Scale or Clinical Global Impressions-Improvement.

Childhood mood disorders

Affective disorders occur at elevated rates in ADHD, and the management of comorbid depressed or irritable/explosive in the context of ADHD represents a particularly difficult clinical challenge. One study to date has examined atomoxetine in adolescents with ADHD and comorbid major depressive disorder (MDD).⁵² Patients were treated for approximately 9 weeks with atomoxetine (≤ 1.8 mg/kg per day) ($n = 72$) or placebo ($n = 70$). While atomoxetine was effective in significantly reducing ADHD symptoms in this depressed sample, Children's Depression Rating Scale-Revised (CDRS-R) score improvement was not significantly different between groups (atomoxetine, -14.8 ± 13.3 ; placebo, -12.8 ± 10.4). Rates of treatment-emergent mania did not differ between groups (atomoxetine, 0.0%; placebo, 1.5%) nor was there spontaneously reported adverse events involving suicidal ideation or suicidal behavior in either group.

In an earlier study by Kratochvil et al⁵³ patients with ADHD and concurrent symptoms of depression or anxiety were randomized to treatment with fluoxetine ($n = 127$) or placebo ($n = 46$) under double-blind conditions for 8 weeks, with concomitant atomoxetine during the last 5 weeks. Depressive symptom reductions according to the CDRS-R were not different between groups. Yet, interestingly, improvement in CDRS-R was significantly greater in subjects with the highest atomoxetine serum levels.

There are limited data to guide the clinician in the management of bipolar disorder (BD) and ADHD. Hah and Chang⁵⁴ reported a consecutive case series on 7 patients with pediatric BD and ADHD who were treated with atomoxetine. The majority (6) of patients were treated concurrently with mood stabilizers. All but 1 patient demonstrated significant improvement in symptoms of ADHD. No patients had episodes of hypomania or mania during the treatment period.

Tolerability

General tolerability

Atomoxetine is generally well tolerated in healthy children and adolescents, with mild adverse effects. Based on data from 6 acute treatment clinical trials (6–9 weeks' duration)

involving 280 younger children ages 6 to 7 years, and 860 older subjects, ages 8 to 12 years, younger children had significantly higher rates of upper abdominal pain, decreased appetite, vomiting, and somnolence (atomoxetine versus placebo [PBO]).¹⁹ Among older children, there were significantly higher rates of decreased appetite, somnolence, irritability, and fatigue observed for those taking atomoxetine versus PBO.¹⁹ In this review, a significant treatment-by-age-group interaction was observed for abdominal pain (younger: atomoxetine = 19%, PBO = 6%; older: atomoxetine = 15%, PBO = 13%; $p = 0.044$), and vomiting (younger: atomoxetine = 14%, PBO = 2%; older: atomoxetine = 9%, PBO = 6%; $p = 0.053$).¹⁹ No new or unexpected safety concerns have been reported over longer-term treatment.²⁴

Enhancing general tolerability; titration, and dosing

Data on atomoxetine treatment and the emergence of adverse events has shown that the frequency of adverse events may depend on method of drug initiation. During initiation of therapy, patients rapidly titrating to 1.2 mg/kg/day over 3 days, as a single daily dose, reported higher rates of spontaneous adverse events than patients on a twice-daily dosing with gradual titration over 3 weeks.⁵⁵ Clinically, some children may tolerate a divided dose well during initiation of treatment, and then be able to switch over to a once-daily dosing schedule for maintenance.

Atomoxetine and growth

In a 5-year safety of treatment study, Spencer et al³⁵ reported on the impact of atomoxetine on growth in a large sample of children and adolescent participants. Maximum decrement of weight loss was observed at 15 months (-9.9% percentage points; $p < 0.001$); however by the 5-year time point, subjects had slightly overshot their starting weight percentile. Similarly, maximum decrement from expected height was observed at 18 mos (-6.6% percentage points; $p < 0.001$). The impact of ADHD pharmacotherapy on growth is an area of ongoing research, including studies of stimulant class and non-stimulant medications, and the consideration of moderating impact of age. However, at present, continuous atomoxetine treatment does not appear to have significant effect on juvenile growth and final stature for most patients.³⁵

Atomoxetine and suicidality

The following boxed warning has been placed (July, 2008) into the package insert for atomoxetine: "Atomoxetine increased the risk of suicidal ideation in short-term studies in

children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Pooled analyses of short-term (6–18 weeks) placebo-controlled trials of STRATTERA in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving STRATTERA compared to placebo. The average risk of suicidal ideation in patients receiving STRATTERA was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials.”

In a meta-analysis of 14 trials on suicide-related behavior in pediatric patients treated with study drug, placebo, or methylphenidate, no ADHD patients being treated with atomoxetine committed suicide.⁴⁵ The frequency of suicidal ideation in patients taking atomoxetine was 0.37% vs 0% in a placebo group. Frequencies between atomoxetine and methylphenidate groups did not differ.⁴⁵

In sum, there is no current evidence that atomoxetine causes suicide in youth. However, consistent with FDA recommendations, clinicians should consider the impact of psychiatric comorbidity, which may be associated with suicidal ideation and/or suicidal behavior. Clinicians should inquire about personal or family histories of mood disorders, as well as clarify whether suicidality has been present before starting atomoxetine. As part of monitoring, clinicians can then inquire about any (negative) changes in mood during treatment, eg, depression, agitation, or worsening of frustration tolerance (in contrast to effective ADHD treatment in which parents will often comment on improved mood, noting that the child is less reactive, irritable or easily frustrated).

Atomoxetine and aggression/psychosis

In a meta-analysis of aggression/hostility-related events from 14 trials of atomoxetine, aggression/hostility-related events occurred in less than 2% of patients and were more frequent in pediatric patients treated with atomoxetine versus placebo (risk ratio of 1.33; not statistically significant). The risk of aggression/hostility events was similar in patients treated with atomoxetine or methylphenidate.⁵⁶ In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.2% (4 patients with reactions out of 1939 exposed to atomoxetine for several weeks at usual doses) of atomoxetine-treated patients compared to 0 out of 1056 placebo-treated patients (Lilly, Product Information, July 2008).

As per the current FDA medication guide, while rare, treatment emergent psychotic or manic symptoms may occur. Therefore, the same principles as described above

apply; clinicians should inquire about personal or family histories of mood disorders and psychosis prior to initiation of atomoxetine. If mood changes occur, inquiry about additional symptoms such as pressured speech, and decreased need for sleep may assist in identifying irritability associated with mania/bipolar disorder, from irritability, which may be more consistent with fluctuating levels of oppositionality.

Atomoxetine and hepatic injury

There have been rare reports of hepatic injury associated with atomoxetine. In an investigation of case reports identified by a computerized search that contained potential hepatic events, of the 7962 pediatric and adult patients treated with atomoxetine in clinical trials, 41 were identified as requiring further analysis. Of those 41 cases, none progressed to liver failure, and most of these events were mild increases in aminotransferase (ALT) and aspartate aminotransferase (AST) levels.⁴⁵ During the 4 years after the market launch of atomoxetine, 351 cases of liver injury were related to the drug treatment for ADHD. Of those 351 cases, 69 had explanations unrelated to the use of the drug, 146 presented insufficient information to assess the cause, 133 contained confounding factors and were labeled as possibly related to drug use, and the remaining 3 cases reported liver injury probably related to atomoxetine use.⁴⁵ The etiology of drug-induced liver injury with atomoxetine may be metabolic idiosyncrasy or induced autoimmune hepatitis.⁵⁷

Given the rare nature of these reports, it is not currently recommended for clinicians to do routine monitoring of liver function tests during treatment, however, families should inform clinicians if they find evidence of liver problems; itching, right upper belly pain, dark urine, yellow skin or eyes, or unexplained flu-like symptoms (Lilly, Product Information, July 2008).

Atomoxetine and the cardiovascular system

There is no current evidence that treatment with therapeutic doses of ADHD pharmacotherapies in healthy children causes serious cardiovascular effects or sudden death.⁵⁸ However, sudden death has been reported in association with atomoxetine treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, atomoxetine generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, and serious heart rhythm (Lilly, Production Information, 2008).

Children who are being considered for treatment with atomoxetine should have a careful clinical history (including assessment for a family history of early sudden death) and physical exam to assess for the presence of cardiac disease, as well as inquiring about possible cardiac symptoms including chest pain and syncope. Electrocardiogram (ECG) is not a mandatory component of cardiovascular assessment and monitoring before and during ADHD pharmacotherapy.^{58,59}

It is well documented that atomoxetine may increase heart rate in both younger (atomoxetine, 8.7 bpm [12.7]; PBO, 1.0 [13.7]; $p = 0.001$) and older (atomoxetine, 6.8 bpm [11.7]; PBO, 0.6 [11.3]; $p < 0.001$) children. A statistically significant treatment-group difference in systolic blood pressure (atomoxetine, 2.1 [9.8] mmHg; PBO, 0.3 [8.1] mmHg; $p = 0.034$) and diastolic blood pressure (atomoxetine, 2.9 [8.2] mmHg; PBO, 0.6 [8.0] mmHg; $p = 0.002$) has been observed for older children, but not for younger children.¹⁹

According to the current FDA medication guide, pulse and blood pressure should be measured at baseline, and periodically while on therapy. Such vigilance may identify certain children at heightened risk. For example, based upon pooled safety data, significantly greater increases in mean pulse rate at endpoint (+3.9 bpm) and in mean diastolic blood pressure (DBP) at endpoint (+1.6 mmHg) have been observed in PMs, as compared to EMs.¹³ In addition, outliers (2.5% in pediatric placebo controlled trials) have been identified, with HR increases >25 bpm; 1.1% had increases in HR of this magnitude on more than one occasion (Lilly, Product Information, July 2008). Significant deviations from baseline vital signs and/or blood pressure in the pre-hypertension or hypertension range can be reviewed with the child's primary care clinician and specialists in pediatric hypertension.

Atomoxetine and CNS toxicity

The rate of seizures as an adverse event with atomoxetine use has been estimated at between 0.1 and 0.2%.⁶⁰ Post-market reports of seizure events were deemed as having no clear contributing or confounding factors, and the rate of report was within the normal population occurrences.⁶⁰

Atomoxetine and overdose

Several studies have examined what happens when a child or adolescent is exposed to an overdose of atomoxetine, based upon poison center reports.^{61–64} Doses to 6.25 mg/kg,⁶¹ to 249 ± 326 mg,⁶² and to 1200 mg⁶³ have been reported. In some reports, adverse drug reactions did not correlate with atomoxetine dose.⁶¹ In others, higher rates of serious outcome were

found with greater maximum dose; >2.8 mg/kg or >200 mg or >4 tablets.⁶⁴ No major outcomes or fatalities have been reported.^{62,63}

However, exposures have caused GI upset, lethargy^{61–63} and seizures in one child,⁶² and seizures in one adolescent female who ingested 2840 mg of atomoxetine in a suicide attempt; serum atomoxetine level of 1995 ng/mL.⁶⁵ Cardiovascular sequela has included sinus tachycardia, and increased blood pressure.^{61–63} Mood adverse effects include agitation;⁶¹ in one study, 17% had acute agitation and were treated with benzodiazepines.⁶³ Despite this apparent safety profile, clinicians should discuss with the patient and family members the importance of taking the atomoxetine doses as prescribed and appropriate monitoring of medications in the home.

Drug–drug interactions

Based upon preclinical data, atomoxetine is metabolized by CYP2D6, but does not induce or inhibit it.¹³ However, CYP2D6 inhibitors may reduce atomoxetine clearance; fluoxetine, paroxetine, and quinidine, all drugs that inhibit CYP2D6, cause higher peak plasma concentrations and slower elimination.⁹ Thus, these CYP2D6 inhibitors may create an iatrogenic virtual PM phenotype in patients with an EM genotype.¹³

Atomoxetine should not be used within 2 weeks after discontinuing MAOI or other drugs that affect brain monoamine concentrations. Atomoxetine should be prescribed with caution if a patient is taking asthma (albuterol or other beta2 agonists), or other medications which could potentiate pressor effects. In addition, there are a few case reports of neurological adverse events when atomoxetine is taken with other drugs; neck-facial twitches/tics with concurrent citalopram,⁶⁶ venlafaxine,⁶⁷ involuntary movements with a stimulant.⁶⁷ In these cases, symptoms resolved after the discontinuation of atomoxetine and other medications.

Summary

Atomoxetine is indicated for both acute *and* maintenance/extended treatment of pediatric ADHD. There is extensive literature on atomoxetine, documenting its pharmacodynamic and pharmacokinetic properties, as well as its short- and longer-term efficacy, the moderating effect of comorbid disorders, and analyses of short- and long-term safety and tolerability. Overall, more children and adolescents have been studied in acute and long-term prospective studies with atomoxetine than with any other pediatric psychotropic in history. To date, over 4000 children have participated in

clinical trials of atomoxetine, including 7 pediatric trials, of which 6 were a randomized, double-blind, placebo-controlled design.^{19,68}

Clinicians and families should be well informed in regards to this evidence base, including the potential for a different profile of clinical response, as compared to stimulant class medications. Atomoxetine's full effects may accrue over months not weeks, and thus patience is necessary in prescribing and administering this medication. We can now point to controlled data demonstrating a near 50% atomoxetine response in children who recently failed a stimulant trial.

While atomoxetine has an overall effect size lower than the first line stimulant class medications in short-term studies, it may be a better drug for an individual child. Given positive preliminary data in some of the more challenging comorbid conditions that occur in children with ADHD (ODD, tics, anxiety and mood disorders, PDD), atomoxetine's role in these more complex patients may continue to emerge.

Finally, the FDA has recommended the development of medication guides, now available for all ADHD pharmacotherapeutic agents, including atomoxetine. Clinicians and families should be familiar with the latest recommendations and consensus, particularly as they apply to areas of cardiovascular safety and the monitoring of mood/behavioral changes and suicidality. The medication guide for atomoxetine can be found at <http://www.fda.gov/cder/Offices/MG/atomoxetineMG/pdf>. Consistent with current clinical consensus that ADHD is a chronic disorder, with impairment into adulthood, further research is warranted, to examine the efficacy and safety of atomoxetine over extended periods of time.

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