



# Atomoxetine in the treatment of children, adolescents and adults with attention deficit hyperactivity disorder

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Atomoxetine hydrochloride (Strattera®), a selective norepinephrine reuptake inhibitor, was the first nonstimulant approved by the US Food and Drug Administration in November 2002, for the treatment of attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults (6 years of age through to adulthood). Atomoxetine is not a controlled substance in the USA or Canada. This article outlines the pharmacology, pharmacokinetics, clinical efficacy and safety of atomoxetine and compares its potential use with other ADHD medications. Recommendations for future research are also made. The efficacy and safety studies of atomoxetine in adults with ADHD led to its approval in the USA and Canada for use in adult ADHD. Among other ADHD medications, atomoxetine has the longest duration of effects. It does not disturb sleep or have potential for abuse. The effectiveness of atomoxetine in managing hyperactivity, impulsivity, inattention, self-esteem, interpersonal and family relationships, and the overall functioning of subjects has been well established in several studies using appropriate scientific methodologies and reliable and valid instruments measuring effectiveness and side effects. The literature provides support for the use of atomoxetine in treating patients with ADHD with diversion and abuse of ADHD medications, tics, anxiety, enuresis, sleep disorders and depressive symptoms. The most common side-effects are appetite suppression, nausea and somnolence in the initial treatment phases. Atomoxetine seems to be well tolerated with a very low discontinuation ratio associated with few side-effects. Future studies may further describe the use and efficacy of atomoxetine in many complicated areas of ADHD and its comorbidities. The combined use of atomoxetine and psychostimulants is a burgeoning area for further research. Atomoxetine may be considered to be the first of a new generation of nonstimulant treatments for ADHD approved for treatment.

Attention deficit hyperactivity disorder (ADHD) is a common disorder of childhood that affects 8 to 12% of children worldwide [1–3]. ADHD continues into adulthood in approximately 70% of cases. Most patients with ADHD have associated impairments in both academic and social functioning [4]. A growing body of data suggest that it is also associated with considerable morbidity and poorer outcomes later in life [3,5–7]. Furthermore, ADHD has a serious impact on developmental stages throughout the life cycle, as described in Figure 1 [8–14].

For many decades, studies have reported that ADHD is transmitted in families [15]. According to twin and adoption studies, the approximate heritability of ADHD has been reported as high as 0.76 (with 1.0 being the highest possible). With the use of new brain imaging techniques including magnetic resonance imaging (MRI) and functional (f)MRI, it has been established that there are functional and anatomical abnormalities in the CNS of children, adolescents and

adults in the frontal–subcortical–cerebellar circuits. However, imaging methods cannot be used as diagnostic tools. The use of genetic tests for diagnosis is also not recommended [3].

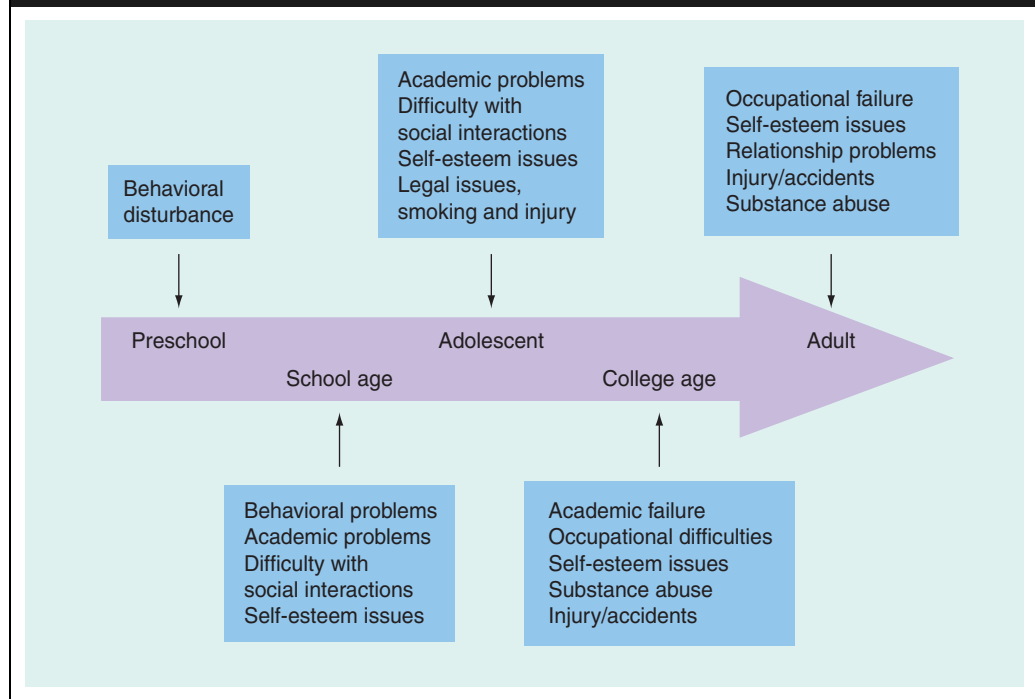
The pathophysiology of ADHD is proposed to involve dysfunctions of the noradrenergic and dopaminergic systems, resulting in difficulties with response inhibition. It has also been proposed that developmentally impaired response inhibition is manifested clinically as persistent and inappropriate impulsivity/hyperactivity and/or inattention [16]. A recent National Institute of Mental Health-funded multimodal treatment study of ADHD (MTA) reported that careful, standardized drug therapy is associated with superior symptom reduction for most children compared with those who received psychosocial interventions alone or no treatment [17]. Evidence also suggests that stimulants (i.e., methylphenidate) that are administered three-times daily (during and after regular school hours) were superior in response compared with

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**Figure 1. The developmental impact of attention deficit/hyperactivity disorder through the life cycle.**



stimulant therapy that was administered twice daily and was restricted to regular school hours [18,19].

### Psychostimulants & other nonstimulant ADHD medications

An integrative approach to ADHD brings together different but interrelated interventions including patient and family education and support, behavioral, cognitive and educational interventions, and individual, group and family counseling with medication for indicated cases [20]. Psychostimulant medications have historically been the first-line medications for ADHD, with reports of use dating back to 1937 for the amphetamine products and 1957 for methylphenidate [21]. Regulatory approval of psychostimulant medication occurred during the 1960s. Stimulants are safe and highly effective medications, with up to 75% of individuals with ADHD responding to the first stimulant selected and a response rate of 80 to 90% if two different stimulants are tried consecutively [22]. Some of the limitations include tolerability, rebound after the desired effects have been observed, insomnia, appetite suppression, limited duration of action (particularly for short-acting stimulants), diversion, abuse risk, and potential for exacerbation of the original or comorbid disorder symptoms. Another major limitation is the refusal of use of

psychostimulants by physicians, patients and their families due to negative publicity, which limits the acceptability and compliance of these medications [23]. The Schedule II status of the stimulants may alarm some patients and families, and has created an inconvenience for both patients and prescribing physicians, as this schedule does not allow for refills without visits to the physician.

Psychostimulants such as methylphenidate (Ritalin®) and dextroamphetamine (Dexedrine®), and their long-acting versions, were the standard and most common drug therapies used in the treatment of ADHD for many years. These medications appear to be quite effective in improving symptoms of inattention, hyperactivity, impulsivity and oppositional behavior. During the last few years there has been major progress in the development of new psychostimulants, extending the duration of effects and improving the delivery system. Table 1 outlines these medications, their pill doses and daily doses. It should be noted that these treatment options are not available in all countries in the world. Long-acting medications are recommended to be used over short-acting medications by national professional organizations such as the Canadian ADHD Resource Alliance [24].

The most common side effects of psychostimulants are sleep, appetite and weight loss or the inability to gain weight, as well as headache,

**Table 1. Long-duration psychostimulants.**

Drug name	Mechanism	Duration (h)	Sprinkle	Maximum daily dose (mg)	Pill doses
Adderall XR®	2 pulse	10.5	Yes	40	5, 10, 15, 20, 25 or 30 mg
Concerta®	3 pulse	12	No	72	18, 36 or 54 mg
Dx Spansule®	1 pulse	5	No	40	5, 10 or 15 mg
Metadate CD®	2 pulse	8–10	Yes	60	20 mg
Metadate ER®	Wax matrix	5–6	No	60	10 or 20 mg
Methylin ER®	Wax matrix	5–6	No	60	10 or 20 mg
Methylphenidate SR®	Wax matrix	5–6	No	60	20 mg
Methypatch®	Transdermal	On skin	No	110	12.5 or 25 cm <sup>2</sup>
Focalin®	Chiral	5–6	No	30	2.5, 5 or 10 mg
Ritalin LA®	2 pulse	8–10	Yes	60	10, 20 or 30 mg
Ritalin SR®	Wax matrix	5–6	No	60	20 mg

stomachache and in some cases, tics. However, there is considerable interest in the use of non-stimulant medications in the treatment of ADHD, as some patients fail to respond to stimulants or are intolerant to them – stimulants are also considered to be controlled substances. A number of compounds, such as antihypertensives (i.e., guanfacine [Tenex®] and clonidine [Catapres®]) or antidepressants (i.e., desipramine and bupropion [Wellbutrin®]), that affect noradrenergic and/or dopaminergic pathways are also efficacious in the treatment of ADHD [25,26]. However, none of these medications are approved by the US Food and Drug Administration (FDA) or regulatory bodies in other countries. There are also limitations in using these medications as their effect on inattention is not as efficacious as stimulants, their management is difficult and there are multiple side effects [20].

Second-line therapies, such as bupropion, the tricyclic antidepressants (TCAs) and  $\alpha_2$ -agonists (i.e., clonidine and guanfacine), maintain some usability in ADHD patients who do not respond well to psychostimulants or atomoxetine. However, concerns over the magnitude of efficacy and/or the tolerability of these medications have limited their use [22]. None of these medications have been approved for the treatment of ADHD by the FDA. The TCAs, which have a primarily noradrenergic effect, have shown moderate-to-robust improvement in ADHD symptoms in 27 out of 29 clinical trials [27]. Although tolerability and concerns regarding the effects on cardiac conduction have limited the use of these

medications, imipramine (Tofranil®) is still occasionally used as a second-line agent. Bupropion has demonstrated a benefit for ADHD symptoms in studies involving children and adults; however, the degree of effectiveness and comparability to other ADHD medications remains questionable [28].

### Pharmacology & pharmacokinetics

The chemical structure of atomoxetine is (3R)-N-methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine hydrochloride. Although the precise mechanism of action is unknown, atomoxetine is reported to enhance noradrenergic function via selective inhibition of the presynaptic norepinephrine transporter [29]. Atomoxetine has little affinity for muscarinic, serotonergic, cholinergic or adrenergic receptors [1]. Peak plasma maximum concentrations ( $C_{max}$ ) are reached approximately 1 to 2 h after dosing [30]. At therapeutic concentrations, 98% of atomoxetine in plasma is bound to protein, primarily albumin [31,32].

For most individuals, the plasma half-life of atomoxetine is approximately 4 h, although 5 to 10% of people have a polymorphism at the cytochrome P (CYP)4502D6 isoenzyme that is associated with a longer plasma half-life.

Atomoxetine was originally known as tomoxetine. The name was changed in order to avoid any confusion with the drug tamoxifen and to prevent potential errors in the dispensing of the medication. Atomoxetine is rapidly absorbed from the gastrointestinal tract, reaching peak levels in 1.83 h in pediatric patients [33] and 1 to 1.5 h in adults [34]. High-fat meals delay the time

to  $C_{\max}$  by approximately 3 h and the rate of absorption by 37%. After absorption, approximately 98% of the drug is bound to albumin [35]. Administering atomoxetine with a meal or snack is generally advised in order to limit gastrointestinal side effects. Atomoxetine is 98% protein bound, distributed into the total body water and ultimately excreted in urine. Atomoxetine is excreted as a glucuronide conjugate [36,37].

In healthy subjects, atomoxetine is metabolized primarily to active 4-hydroxyatomoxetine by the hepatic isoenzyme CYP2D6. This metabolite is equipotent to atomoxetine as a norepinephrine transport inhibitor. Approximately 7% of Caucasians and less than 1% of the Asian population are poor CYP2D6 metabolizers and this polymorphism results in altered atomoxetine pharmacokinetics [38]. Oral bioavailability is reduced (63% in extensive metabolizers and 94% in poor metabolizers) and the estimated half-life is extended (5.2 h in extensive metabolizers and 21.6 h in poor metabolizers). As expected, slow metabolizers demonstrate higher peak plasma concentrations (five-times higher) than extensive metabolizers. However, safety and efficacy studies to date do not indicate a need to change the dose or administration schedule based on the patient's metabolic status [39]. Caution is still advised when combining atomoxetine with medications that inhibit the CYP2D6 enzyme system. The combination of atomoxetine and a CYP2D6 inhibitor, such as paroxetine (Paxil®) or fluoxetine, can lead to an increase in steady-state plasma concentrations of atomoxetine. When combined with fluoxetine, the peak plasma levels of atomoxetine increased by approximately threefold [40].

Atomoxetine is a potent inhibitor of the presynaptic norepinephrine transporter, with minimal affinity for other noradrenergic receptors, other neurotransmitter transporters or receptors. The clinical profile of atomoxetine appears to differ from that of stimulants and it is being studied as a potential treatment for ADHD. Several reports have provided evidence that atomoxetine is superior to placebo in reducing the symptoms of ADHD in children and adults [41–43].

It has been hypothesized that as atomoxetine does not increase dopamine in the nucleus accumbens it would have less impact on the reward center and be less abusable, and thus, as it does not increase dopamine in the striatum, it would not worsen tics. Both of these hypotheses were later demonstrated empirically [29].

It has also been suggested that atomoxetine may have a better impact than psychostimulants in treating patients with substance abuse and tic disorders (Figure 2) [29].

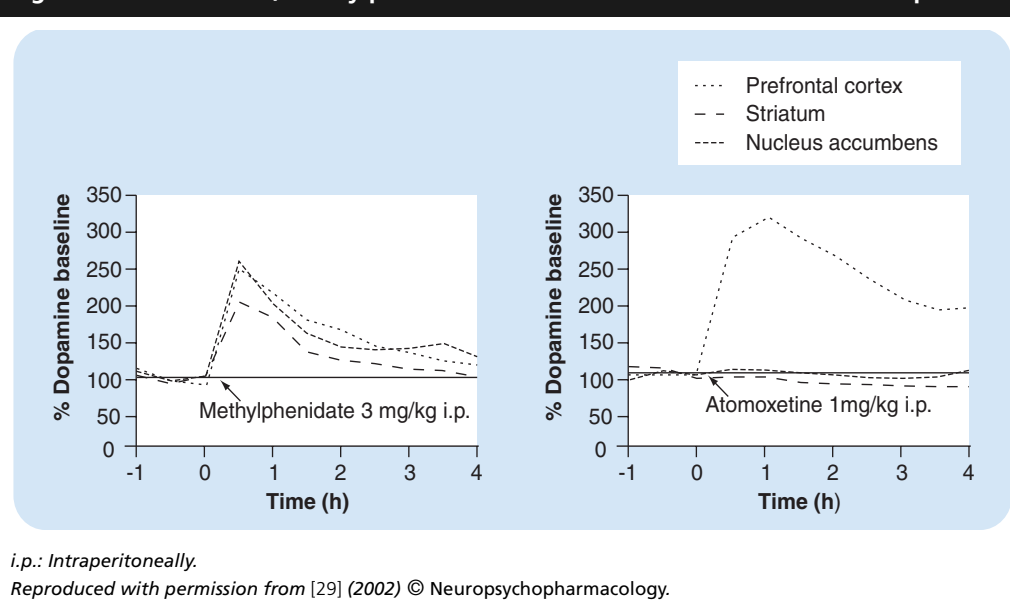
### Atomoxetine clinical studies

Atomoxetine, a selective noradrenaline reuptake inhibitor, is the only nonstimulant medication approved by the FDA for the treatment of ADHD; it is also the only pharmacotherapy approved for the treatment of adults with ADHD. The first atomoxetine studies were performed with adults. To date, there have been two open-label and seven randomized, double-blind, placebo controlled trials with atomoxetine (three in adults and six in children and adolescents have been published). Each of these trials has demonstrated that atomoxetine was superior to placebo [44]. The effectiveness of atomoxetine in the treatment of ADHD has been reported among children and adolescents when administered once or twice daily [39,41,43,44].

The effectiveness and tolerability of atomoxetine in the treatment of children, adolescents and adults involved more than 4000 subjects, of whom more than 1100 subjects have been followed up for more than 6 months, some for as long as 3.5 years. Outcomes on psychosocial measures including functional and quality of life (QoL) measures, such as the Child Health Questionnaire (CHQ), a parent-rated health outcome scale that measures physical and psychologic well-being), provides evidence that the improvements in ADHD symptoms associated with atomoxetine are associated with better family and social functioning during acute therapy [39] and long-term (24-month) treatment [46].

Two large, randomized, double-blind, placebo-controlled, 10-week studies of atomoxetine in a total of 536 adults with ADHD found atomoxetine superior to placebo in the reduction of ADHD symptoms in adults and treatment effect sizes for primary outcome measures were comparable with those observed in other large efficacy studies in adult psychiatric disorders such as depression [40].

A randomized, open-label, 10-week study of 228 children with ADHD revealed evidence that the magnitude of treatment response (reduction of inattention and hyperactive/impulsive symptoms) associated with atomoxetine administration and its tolerability were comparable with that observed with methylphenidate. Subjects treated with atomoxetine

**Figure 2. Atomoxetine, methylphenidate and their effects on extracellular dopamine.**

reported more vomiting and somnolence, whereas patients treated with methylphenidate reported more insomnia [47].

One of the major advantages of atomoxetine compared with other ADHD medications is its long duration effect, which controls behavior problems and inattention early in the mornings and late in the evenings. Results of a randomized, placebo-controlled, 8-week trial of once-daily atomoxetine in a total of 197 children with ADHD (aged 6–12 years) revealed that efficacy on children's evening and early morning home behaviors (assessed by Daily Parent Rating of Evening and Morning Behavior-Revised and the Connor's Global Index-Parent Evening Scale), persists into the evening and the following early morning [42].

The following section will review the major studies establishing effectiveness and safety of atomoxetine in historic order.

A randomized, placebo-controlled study of atomoxetine once daily for children and adolescents with ADHD reported that atomoxetine appeared to be as effective when the daily dose was administered in the morning, as when the dose was divided and administered in the morning and evening. This finding has been observed in previous studies, and is particularly compelling, given that the half-life of this drug is approximately 5 h for most patients, and suggests that the effects of atomoxetine on ADHD symptoms persist beyond its immediate direct pharmacologic effects [32]. If verified, this is of particular interest as it suggests a marked

difference from the stimulants, the effects of which are generally closely correlated with plasma drug levels [48]. This finding is very important as atomoxetine appears to provide for the control of ADHD symptoms in the evening hours without disturbing sleep.

A double-blind, randomized, placebo-controlled trial with 197 children, 6 to 12 years of age, reported that once-daily dosing in the morning was associated with significant symptom reduction that persists into the evening and the morning hours [42].

In the first published clinical paper on atomoxetine, the research team assessed the experimental noradrenergic compound tomoxetine as an alternative for adult ADHD [43]. They conducted a double-blind, placebo-controlled, 3-week crossover study of tomoxetine in 22 adults with well-characterized ADHD. To assess the change during treatment, the authors used the DuPaul 14-item ADHD rating scale (RS) on a severity grid, the Hamilton Depression RS and the Beck Depression inventory to assess depression and the Hamilton Anxiety RS to assess anxiety. In addition, the patients underwent a neuropsychologic battery that included an auditory Continuous Performance Test (CPT), Stroop Color Word tests, the computerized Wisconsin Card Sorting Test (WCST) and the Rey-Osteriech Complex Figure test (Rey-O). The study design included two 3-week treatment periods separated by 1 week of wash-out. The study medication was titrated up to 40 mg/day by week 1, 80 mg/day (40 mg twice

daily) by week 2 and maintained at 80 mg/day by week 3 unless adverse effects emerged. The treatment with tomoxetine in an average oral dose of 76 mg/day was well tolerated. There were no serious adverse events, with the exception of one patient who reported symptoms of severe anxiety while receiving tomoxetine and was subsequently removed from the study. In all, 21 out of 22 patients completed the study. A preestablished definition of improvement of more than 30% reduction in symptoms was adopted for the purposes of the study. The most notable effects were observed on symptoms of inattention. The authors found no meaningful associations between improvement of ADHD symptoms and gender, socioeconomic status and/or positive family history of psychiatric disorders. However, there was a trend toward greater rates of improvement in ADHD patients who had no comorbid disorders. Examination of the effects of tomoxetine on measures of depression and anxiety failed to reveal a meaningful change over time. Drug-specific improvement in ADHD symptoms was highly significant overall and sufficiently robust to be detectable in a parallel-groups comparison restricted to the first 3 weeks of the protocol. Of the 21 patients, 11 showed improvement after receiving tomoxetine, compared with only two who improved after receiving placebo. The magnitude of response to tomoxetine treatment (52%) approximates the average improvement rate observed in previous, methodologically similar trials of methylphenidate and desipramine, completed by the same authors. Significant tomoxetine-associated improvement was noted on neuropsychologic measures of inhibitory capacity from the results of the Stroop tests. The authors concluded that this preliminary study provided support for further investigations of tomoxetine over extended periods of treatment.

A multicenter study conducted at 13 outpatient investigative sites in the USA compared the efficacy of three doses of atomoxetine with placebo in children and adolescents with ADHD [39]. The study was also aimed at measuring the positive impact of the medication on the overall psychologic and social functioning of patients as well as the impact on their self-esteem. Children and adolescents who were 8 to 18 years of age were eligible to participate in the study, if they met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for ADHD. Each child was assessed using

clinical examinations and diagnosis was further confirmed by a structured interview (the behavioral module of the Kiddie Schedule for Affective Disorders and Schizophrenia for school aged children – Present and Lifetime Versions [KSADS-PL] developed by Kaufman and colleagues [49]. It was also required that each study participant have a symptom severity score at least 1.5 standard deviations (SDs) above age and gender norms on the ADHD RS-IV Parent Version (investigator administered and scored) in their total score, or on the inattentive or the hyperactive/impulsive subscales [50]. Patients were assessed for concurrent depression and anxiety with the KSADS-PL depression and anxiety modules. Important exclusionary criteria included an IQ of less than 80 (assessed by the Wechsler Intelligence Scale for Children, Third Edition), serious medical illness, comorbid psychosis or bipolar disorder, history of seizure disorders, or ongoing use of psychoactive medications other than the study drug. After an initial 12- to 18-day evaluation and medication washout period, patients were randomized to one of three doses of atomoxetine (0.5, 1.2 or 1.8 mg/kg/day) or placebo for approximately 8 weeks. Visits were weekly for the first 4 weeks and biweekly thereafter. All patients in the atomoxetine groups began treatment at 0.5 mg/kg/day. In the higher dose groups, the drug was titrated with intermediate steps of 0.8 and 1.2 mg/kg/day at 1-week intervals. The middle and upper doses were chosen to bracket the final mean atomoxetine dose (1.5 mg/kg/day) of two previous placebo-controlled trials that used dose titration based on clinical response. In addition, the upper dose was lower than the highest doses studied in clinical pharmacology studies of healthy adult CYP2D6 extensive and poor metabolizers. The study drug was administered as equally divided doses in the morning and late afternoon. The drug was identical in appearance for all treatment groups. Patients were randomized using computer-generated codes via an interactive voice response system. The protocol-specified primary outcome measure was the ADHD RS, an 18-item scale based on a semi-structured interview with the patient's parent (or primary caregiver). Each item corresponded to one of the 18 DSM-IV criteria. This scale has been studied and found to have satisfactory psychometric properties [51]. Other assessment tools included the hyperactivity/impulsivity and inattention subscales of the ADHD RS, the Conners' Parent RS-Revised: Short Form (CPRS-R) and Clinical Global Impressions of Severity

(CGI-S) [52–54]. Affective symptoms were assessed using the revised Children's Depression RS Revised (CDRS-R) [55]. Broader social and family functioning was assessed using the CHQ, a parent-rated health outcome scale that measures physical and psychosocial wellbeing. The psychometric properties of the CHQ have been studied and normative data have been reported [56]. Safety and tolerability were assessed by open-ended questioning for adverse events, in addition to the regular monitoring of vital signs and laboratory data. In order to assess symptom severity at the end point relative to an unaffected population, scores were analyzed on the primary outcome measure as t-scores. These represent a transformation based on normative data adjusted for gender and age. In a normal population, a t score of 50 represents the mean score and a deviation of 10 points in either direction represents 1 SD from the mean. It was reported that atomoxetine was superior to placebo in reducing ADHD symptoms and in improving social and family functioning. Atomoxetine was associated with a graded dose-response and 1.2 mg/kg/day appeared to be as effective as 1.8 mg/kg/day, and both are likely to be an appropriate initial target dose for most patients. Treatment with atomoxetine was found to be safe and well tolerated.

Two identical, multicenter studies conducted at 17 sites in the USA compared the safety and efficacy of atomoxetine with placebo and methylphenidate [16]. Structured and semistructured interviews were used to ensure that patients were meeting ADHD symptom and symptom severity criteria. In this study, patients were stratified based on prior history of treatment with any psychostimulant (stimulant naive [SN] and stimulant prior exposure [SPE]), then randomized to 9 weeks of active treatment. Methylphenidate was included as a SN stratum comparator to validate the study design. Dosing with atomoxetine (which was known as as tomoxetine then) was titrated in divided doses (before and after school) based on safety and efficacy to a maximum dose of 2.0 mg/kg/day. The primary efficacy analysis was an intent-to-treat comparison of atomoxetine versus placebo of the combined strata using the ADHD RS, administered and scored by the investigator, based on parent assessment. In the two studies, 147 patients (65 atomoxetine, 62 placebo and 20 methylphenidate) and 144 patients (64 atomoxetine, 62 placebo and 18 methylphenidate) were randomized to treatment. In each study, atomoxetine demonstrated statistically and clinically significantly greater reduction

in the severity of ADHD symptoms than placebo ( $p < 0.01$ ). It was concluded that the data from these studies provided convincing evidence of efficacy of atomoxetine in the treatment of ADHD in pediatric patients, regardless of subtype. It was reported that atomoxetine was safe and well tolerated and compared favorably with methylphenidate on both efficacy and safety.

Two identical, double-blind, placebo-controlled trials reported on the safety and efficacy of atomoxetine for ADHD [57]. The patients included in this study had a score on the ADHD RS that was at least 1.5 SDs above the age/gender norm for their diagnostic subtype or for the mixed subtype. The reduction in ADHD symptoms with atomoxetine was not significantly different from the reduction of symptoms with methylphenidate. The only adverse event that had a higher prevalence in the atomoxetine group than the placebo group was anorexia. It was reported that the efficacy of atomoxetine was consistent across multiple subgroups of patients with or without earlier exposure to stimulants as well as in patients with inattentive and mixed types of ADHD. Benefits from the medication were observed as early as the first week. Only 4.7% of the patients discontinued the study. It was also important to find that 27% of the patients treated with methylphenidate, 8.9% of the patients who took placebo and 7.0% of the patients on atomoxetine reported insomnia; the difference between methylphenidate and atomoxetine was statistically significant.

The long-term safety and tolerability of atomoxetine treatment was examined in 325 patients (7–17 years of age) for an extended treatment period of up to 78 weeks [58]. The study reported that only 12 out of the total 325 patients (3.7%) discontinued the medication due to an adverse event. It was concluded that atomoxetine was well tolerated in this long-term clinical trial. In contrast to acute studies where mean weight loss was observed, this study revealed that mean weight increased during long-term therapy. Effects on electrocardiograph (ECG) parameters were consistent with an increased heart rate. There was no evidence for drug-related QTc prolongation.

An open, prospective, dose-ranging study of atomoxetine monotherapy in the treatment of 30 children with ADHD between the ages of 7 and 14 years examined the tolerability and effectiveness of atomoxetine in the treatment of children with ADHD [59]. Atomoxetine was started at 10 to 20 mg/day and titrated weekly up to

90 mg over 11 weeks, depending on response and adverse effects [59]. A total of 22 children completed the full 11 weeks. The investigators assessed the efficacy with weekly clinician and parent ratings of ADHD and oppositional symptoms and monitored adverse effects, laboratory findings and cardiovascular parameters. It was reported that treatment with atomoxetine (mean final total daily dose of 1.9 mg/kg/day) was very well tolerated without meaningful adverse events. It was found that atomoxetine significantly reduced core symptoms of ADHD in all but one patient on the 18 individual items in the ADHD RS-IV. It was reported that more than 75% of subjects who completed 10 weeks of treatment showed a greater than 25% decrease in ADHD symptoms.

In a randomized clinical study with atomoxetine, a total of 228 patients (7–15 years of age) were given atomoxetine ( $n = 184$ ) or methylphenidate ( $n = 44$ ) for 10 weeks [60]. The visits were weekly, with an ascending dose titration completed based upon the clinician's impression of efficacy, safety and tolerability. The primary efficacy measure was the ADHD RS-IV Parent Version: Investigator administered and scored. The total score, inattention subscale and hyperactivity/impulsivity subscale were presented as t-scores. The CPRS-R was also used, along with CGI of ADHD Symptoms (CGI-ADHD-S). For each efficacy measure, change from baseline to end point was computed using a last observation carried forward approach. Safety was assessed utilizing open-ended questions. Children in both groups displayed marked improvement in inattentive and hyperactive/impulsive symptom clusters. For both groups, mean ADHD RS t-scores at end point approached age and gender norms. For both medications, inattentive and hyperactive/impulsive symptoms responded to treatment and parent reports were consistent with investigator assessments. Safety and tolerability were also similar between the two treatment groups, with few discontinuations due to adverse events. Atomoxetine was found efficacious and well tolerated in ADHD children and provided preliminary evidence that the magnitude of reduction of core ADHD symptoms and degree of tolerability were found to be comparable to that observed with methylphenidate.

In a double-blind study, 171 children and adolescents (age range: 6–16 years) were randomly assigned to receive 6 weeks of treatment

with atomoxetine or placebo administered once daily to assess the efficacy of atomoxetine [32]. Outcomes among atomoxetine-treated patients were superior to those of the placebo treatment group as assessed by investigator, parent and teacher ratings. The treatment effect size (0.71) was similar to those observed in previous atomoxetine studies that used twice-daily dosing. Parent diary ratings suggested that drug-specific effects were sustained late in the day. Discontinuations due to adverse events were low (<3%) for both treatment groups and no serious safety concerns were observed. It was concluded that once-daily administration of atomoxetine is an effective treatment for children and adolescents with ADHD.

A double-blind, placebo-controlled trial of atomoxetine for children with ADHD was conducted at 12 outpatient sites in the USA [42]. A total of 197 children, 6 to 12 years of age, who had been diagnosed with ADHD on the basis of the American Psychiatric Association (APA)'s DSM-IV, were randomized to receive 8 weeks of treatment with atomoxetine or placebo once daily in the mornings. The symptoms were assessed with parent and investigator rating scales based on the 18 diagnostic criteria items of ADHD. Daily parent assessments of children's home behaviors in the evening and early morning were recorded. This instrument measures 11 specific morning and evening activities, including getting up and out of bed, doing and completing homework and sitting through dinner. In this study, an early dose titration was used, with patients receiving a starting atomoxetine dose of 0.8 mg/kg/day for the first 3 days and then a dose of 1.2 mg/kg/day for the remainder of the first week. Once-daily doses of atomoxetine (final mean daily dose of 1.3 mg/kg) was significantly more effective than placebo in treating core symptoms of ADHD. Mean reductions in the ADHD RS parent version total score were significantly greater for patients randomized to atomoxetine, beginning at the first visit after the initiation of treatment and continuing for all subsequent visits. Both inattentive and hyperactive/impulsive symptoms were significantly reduced with atomoxetine compared with placebo. With continued treatment and dose titration, core symptoms of ADHD continued to decrease throughout the 8-week study. Efficacy outcomes for the evening hours for atomoxetine-treated patients were superior to those for placebo-treated patients. Decreases in the daily parent assessment morning subscores at end point



showed a significant reduction in symptoms that lasted into the mornings. Adverse events reported to be more significantly decreased included appetite, somnolence and fatigue. As reported in previous once-daily administration studies, these events and other gastrointestinal events were self-limiting, peaking at 1 to 3 days of treatment and declining thereafter. Atomoxetine treatment was found to be effective and safe. The majority of atomoxetine-treated patients (80.5%) completed treatment and the rate of discontinuations as a result of adverse events were low (4.5%).

A global multicenter study conducted at 33 academic investigative centers in Europe (24 centers), Israel (two centers), South Africa (four centers) and Australia (three centers) in children and adolescents who responded to an initial 12-week, open-label period of treatment with atomoxetine, were randomized to continued treatment or placebo for 9 months under double-blind conditions [61]. The study documented that a total of 416 patients completed acute atomoxetine treatment and were randomized. At end point, atomoxetine was superior to placebo in preventing relapse defined as a return to 90% of baseline symptom severity (proportion relapsing with atomoxetine: 65 of 292 [22.3%]; placebo: 47 of 124 [37.9%];  $p = 0.002$ ). The proportion of patients with a 50% worsening in symptoms postrandomization was also lower on atomoxetine (83 of 292 [28.4%] vs placebo: 59 of 124 [47.6%];  $p < 0.001$ ). Compared with patients in the placebo group, atomoxetine-treated patients had superior psychosocial functioning at end point. Discontinuations for adverse events were low in both groups and tolerability was similar to that observed in acute treatment trials. The authors concluded that in patients who responded favorably to 12 weeks of initial treatment, atomoxetine was superior to placebo in maintaining response for the ensuing 9 months. The study supported the use of extended use of atomoxetine in the treatment of children and adolescents.

A recent clinical study assessed the tolerability and safety of atomoxetine combined with fluoxetine as well as the value of atomoxetine as a monotherapy for ADHD in the presence of depression or anxiety [62]. The study compared atomoxetine alone with atomoxetine plus fluoxetine in children with ADHD and comorbid mood or anxiety symptoms. Safety and effectiveness of atomoxetine monotherapy compared with fluoxetine ( $n = 127$ ) or placebo ( $n = 46$ ) under double-blind conditions for 8 weeks,

with concomitant atomoxetine use the last 5 weeks. At end point, reduction in ADHD, depressive and anxiety symptoms were marked for both treatment groups. Some differences between treatment groups for depressive symptoms were significant; however, the magnitudes of the differences were small and likely to be of limited clinical importance. The combination group had greater increases in blood pressure and pulse than did the monotherapy group. It was concluded that in pediatric patients with ADHD and comorbid symptoms of depression or anxiety, atomoxetine monotherapy appears effective for treating ADHD. Anxiety and depressive symptoms also improved; however, the authors cautioned that in the absence of a placebo-only group, it was not possible to conclude that these were specifically the result of treatment with atomoxetine. They also reported that combined atomoxetine/fluoxetine therapy was well tolerated.

A recent multicenter study focused on the use of plasma concentration to guide atomoxetine doses in ADHD patients [63]. Following approximately 6 weeks of open-label treatment with atomoxetine (1.2 mg/kg/day), ADHD patients aged 6 to 16 years with suboptimal responses and peak plasma concentrations equal to or less than 800 ng/ml were randomly assigned to a 4-week, double-blind period either to remain at 1.2 mg/kg/day (ATX12,  $n = 62$ ) or to receive 1.8 mg/kg/day (increased to 2.4 mg/kg/day if nonresponsive after 2 weeks [ATX18/24];  $n = 63$ ). Initial period open-response rates for patients with plasma concentrations less than 800 ng/ml were significantly higher than for patients with concentrations equal to 800 ng/ml (60.5 vs 37.3%;  $p = 0.008$ ). The double-blind period final mean doses for the ATX118/24 and ATX12 groups (respectively) were 2.1 and 1.1 mg/kg/day; however, final mean plasma concentrations remained below 800 ng/ml. Response rates were not significantly different across treatment groups. The authors concluded that while the results suggest that raising plasma concentrations above 800 ng/ml may enhance improvements, further studies are still required.

As the above reviews indicate, the therapeutic effects of atomoxetine and methylphenidate, as compared with placebo, are similar. The average effect size in the meta-analysis of 62 controlled methylphenidate trials in nearly 2900 children and adolescents was 0.78 with teacher ratings and 0.54 with parent ratings [64].

### Effectiveness in treating comorbid disorders associated with ADHD

As indicated earlier, comorbidity is almost always the rule rather than the exception in ADHD. Preliminary evidence indicates that atomoxetine is similarly effective for ADHD with concurrent symptoms of depression and anxiety [65]. Atomoxetine may reduce depressive symptoms as indicated by a reduction of the CDRS-R scores. Positive outcome on the self-esteem subscale of the CHQ have been reported [39]. A recent study comparing the positive effects of controlling depressive symptoms with atomoxetine and placebo versus atomoxetine and fluoxetine in pediatric patients reported that atomoxetine monotherapy appears effective for treating ADHD and comorbid symptoms of depression and/or anxiety [62].

In children with ADHD with comorbid oppositional defiant disorder, atomoxetine was found effective in treating the symptoms of both [66]. Atomoxetine was also found to be effective in decreasing tic frequency and severity in a double-blind, placebo-controlled 18-week trial in 148 children and adolescents with ADHD and tic disorders [67].

The recent papers and posters presented in international meetings and abstracted for reviews demonstrate that there is an increasing interest in studying the effects of atomoxetine in treating not only ADHD core symptoms (inattention, hyperactivity and impulsivity) but also commonly associated behavioral, mood and anxiety symptoms and/or disorders. Furthermore, atomoxetine has been found effective in reducing tics and ADHD symptoms [68].

In a recent study of children with ADHD comparing the effects of atomoxetine and methylphenidate on sleep, it was reported that patients on atomoxetine reported shorter time-to-sleep onset and more normal sleep relative than those on methylphenidate, as described by measures such as actigraphy, polysomnography, and child and parent diaries [69].

A clinical study evaluated 500 adults from 31 sites in the USA [70]. The Wender Reimherr Adult Attention Deficit Disorder Scale measures temper, affective ability and emotional over-reactivity and assesses emotional dysregulation. It was reported that adult ADHD patients with symptoms of emotional dysregulation had marked improvement in symptoms of ADHD on atomoxetine compared with placebo.

A recent study reported the positive effects of atomoxetine on QoL [71]. CHQ is a QoL measure including three psychosocial and four physical domains. The scale also reviews individual and family functioning. Atomoxetine had significantly greater improvement than placebo on all seven domains. In addition, atomoxetine was effective in subgroups of patients identified as having more severe psychosocial impairment.

In summary, atomoxetine efficacy and safety studies supported the approval of the medication by regulatory bodies and provided reassurance for use in children, adolescents and adults with ADHD. The long duration of effect, claimed to be as high as 24 h, and positive control of ADHD symptoms extending into the evening hours, decreased abuse potential as compared with psychostimulants. Comparable effect size to psychostimulants also provided a good alternative to psychostimulants and tricyclics. Both atomoxetine and psychostimulants appear to be effective as first-line medications. The choice between these two types of drugs will be determined by careful review of patient characteristics, duration of symptoms, earlier medication response and history of side effects to the medication, as well as the nature of the associated symptoms and disorders. The cost, presence or absence of third-party payments and positive or negative patient, family and physician biases towards these medications may also play a role in the selection. One of the most important advantages of psychostimulants over atomoxetine is a long history of use since 1937. It is hoped that atomoxetine will also be found effective and safe in the long-term follow-up over the next few decades.

### Dosing

Table 2 outlines the recommended dosing for on atomoxetine [72]. Although some patients show a very positive response to treatment within the first days and weeks after initiation, other patients may exhibit positive treatment response only a few weeks after starting the initial dose. This feature of atomoxetine seems to be different than psychostimulants.

After the initiation of the first dose, waiting approximately 10 days before making further dose increases may decrease the risk of side effects, particularly gastrointestinal complaints and somnolence. Onset of action of atomoxetine is generally evident in 1 to 2 weeks, with a clinically significant therapeutic effect in 2 to 4 weeks. Patients should be well informed so that they do not

**Table 2. Recommended dose titration for atomoxetine in children and adolescents\*.**

Body weight (kg)	Starting dose (~0.5 mg/kg/day)	Intermediate dose (~0.8 mg/kg/day)	High dose (~1.2 mg/kg/day)
20–29	10	18	25
30–44	18	25	40
45–64	25	40	60
≥65	40	60	80

\*Maximum recommended dose 1.4 mg/kg/day or 100 mg, whichever is less.

Adapted from [72].

expect immediate results. Patients may continue to experience symptom improvements even beyond the fourth week (Box 1) [63].

### Atomoxetine & abuse potential

During the initial safety trials, atomoxetine's abuse potential was compared with methylphenidate. In a study of 16 nondependent, recreational drug users, it was reported that atomoxetine had no pleasurable subjective drug effects based on Visual Analog Scales (VAS), Addiction Research Center Inventory (ACRI) or Adjective Rating Scales (ARS). These measures were given prior to administration of placebo, atomoxetine (20, 45 and 90 mg) or methylphenidate (20 and 40 mg) and at seven intervals following the administration over the course of 4 h. Mean scores over this period indicated that high-dose atomoxetine resulted in increased bad and sick VAS and ACRI responses, whereas 40 mg of methylphenidate increased good scores on VAS, ACRI and ARS [73]. In current clinical trials, there has not been evidence of symptom rebound and adverse events suggestive of a drug-discontinuation or withdrawal syndrome when atomoxetine is abruptly discontinued [35].

### Box 1. Guidelines in atomoxetine dosing for children 6 years of age and over, and adolescents up to 70 kg.

- Initiate at a total daily dose of approximately 0.5 mg/kg. Maintain for a minimum of 10 days.
- If patients have not experienced clinically significant symptom response at the initial dose, increase to the intermediate dose level. Maintain for a minimum of 10 days.
- According to clinical response and tolerability, the dose may then be increased to 1.2 mg/kg/day.
- After a minimum of 30 days, dose should be reassessed and adjusted according to clinical response and tolerability.
- The total daily dose in children and adolescents up to 70 kg should not exceed 1.4 mg/kg or 100 mg, whichever is less.

Adapted from [72].

### Side-effect profile

The safety and tolerability of atomoxetine have been evaluated in several clinical trials and the available data do not suggest any serious safety concerns. Atomoxetine has generally been well tolerated [32,40,59,61,62]. Overall drug-discontinuation rates were low in both groups (atomoxetine 2.3%, placebo 1.2%). Cardiovascular effects of atomoxetine (subtle increases in both heart rate and blood pressure) appear to be clinically insignificant. No effect on the QTc interval was observed [74–76].

Along with stimulants, atomoxetine may be associated with a brief period of decreased appetite and weight loss upon initiation (14.1 vs 5.8% placebo) [76]. Controlled long-term studies are not yet available to confirm these findings. Other side effects of atomoxetine include dry mouth, insomnia, constipation, vomiting, dizziness, fatigue, nausea, dyspepsia and mood swings. In addition, urinary retention and sexual dysfunction have been observed in adult patients. Most of these adverse effects diminish over the first months of treatment. Atomoxetine has also been associated with mydriasis and, therefore, should not be used in patients with narrow angle glaucoma. Hypersensitivity reactions appear to be rare [74–76]. Unlike stimulants, available data on atomoxetine does not show any potential for abuse. The safety profile and/or efficacy of atomoxetine appear to be favorable when compared with other nonstimulant medications for ADHD such as TCAs, bupropion and venlafaxine.

An analysis of the pooled adverse event data reported at least 5% of patients taking atomoxetine in four of the early, double-blind, placebo-controlled trials [76]. Decreased appetite was the most common adverse event with atomoxetine use, occurring in approximately 14% of the subjects on atomoxetine compared with 6% on placebo. Other statistically significant adverse events were vomiting and dizziness. Blood

pressure and heart rate were mildly increased; however, these were not found to be clinically significant. Discontinuations of atomoxetine in the pediatric placebo-controlled trials were not significantly different from placebo (atomoxetine 3.8%, placebo 1.4%;  $p = 0.125$ ). Discontinuations that did occur were most often related to decreased appetite, sleep disturbances and anxiety or nervousness. There was no evidence of symptom rebound or of acute discontinuation syndrome, therefore tapering of atomoxetine did not appear to be a problem when discontinuing treatment. Reviews concerning the adult side effect profiles showed that adults show more noradrenergic side effects.

Adverse effects on the cardiovascular system, including abnormalities in heart rate, blood pressure or cardiac rhythm have been associated with several noradrenergic medications.

The magnitude and impact of blood pressure and pulse elevations in patients taking atomoxetine encourages clinicians of its safe use [76]. Short-term cardiovascular safety in children, adolescents and adults with ADHD was assessed in five randomized, double-blind trials (duration  $\leq 10$  weeks) with atomoxetine ( $n = 612$ ) or placebo ( $n = 474$ ). Long-term cardiovascular safety in children and adolescents ( $n = 169$ ) was assessed in patients who entered an open-label extension or a blinded continuation following short-term treatment. Adverse events, blood pressure, sitting pulse and ECGs were collected throughout the trials. QT intervals were corrected for heart rate by a data-specific correction factor (QTcD, derived from baseline ECGs) as well as standard methods. Atomoxetine treatment was associated with small but statistically significant increases in mean systolic blood pressure in adults and diastolic blood pressure in children and adolescents. Mean pulse rate increased for all atomoxetine treatment groups. Adults had statistically significant increases in mean systolic blood pressure in adults receiving atomoxetine (2.9 mmHg;  $p = 0.002$ ) but not diastolic blood pressure (1.8 mmHg;  $p = 0.083$ ). A mean pulse increase of 5.3 beats/min ( $p < 0.001$ ) was observed in subjects taking atomoxetine compared with placebo.

The increases in blood pressure and pulse tended to occur early in therapy, stabilized and returned toward baseline upon drug discontinuation. There were no significant differences between atomoxetine and placebo treatment groups in change in QTcD interval for all study populations. Palpitations in the adult patient population were

the only significant cardiovascular adverse event ( $p = 0.037$ ) occurring more frequently in the atomoxetine-treatment group (3.7%) than in the placebo group (0.8%). Discontinuations due to cardiovascular-related events were very uncommon in the adult group and did not occur in the child/adolescent group. As atomoxetine had noradrenergic activity similar to many other ADHD medications, increases in pulse and blood pressure were small and little, if any, clinical significance can be expected. In adult patients with borderline or high blood pressure, close monitoring of blood pressure is important. Atomoxetine was not associated with QT interval prolongation. Cardiovascular effects of atomoxetine were minimal and atomoxetine was well tolerated in short- and long-term treatment [32,40,59,61–63,74–76].

### FDA warning concerning atomoxetine & suicidal ideation

The FDA has issued a public health advisory entitled *Suicidal thinking in children and adolescents being treated with Strattera (Atomoxetine)* and directed Eli Lilly and Co., the manufacturer of atomoxetine, to revise the labeling for this product to include a boxed warning and additional warning statements that alert health care professionals to an 'increased risk of suicidal thinking in children and adolescents treated with this drug'. The increased risk of suicidal thinking for this drug was identified in a combined analysis of 12 short-term (6–18 weeks) placebo-controlled trials (11 in ADHD and one in enuresis). These 12 trials involved a total of 2200 patients, including 1357 receiving atomoxetine and 851 receiving placebo. The FDA advisory reported that the analysis showed a greater risk of suicidal thinking during the first few months of treatment in those receiving atomoxetine. The average risk of suicidal thinking was approximately four/1000 patients treated with atomoxetine compared with no events in placebo-treated patients. There was one suicide attempt among 2200 patients, occurring in a patient treated with atomoxetine. Based on these data, the FDA has determined that the following points are appropriate for inclusion in the boxed warning;

- Atomoxetine increases the risk of suicidal thinking in children and adolescents with ADHD
- Anyone considering the use of atomoxetine in a child or adolescent for ADHD must balance the increased risk of suicidal thinking with the clinical need for the drug

- Patients who are started on therapy should be observed closely for clinical worsening, suicidal thinking or behaviors, or unusual changes in behavior
- Families and caregivers should be advised to closely observe the patient and to communicate changes or concerning behaviors with the prescriber
- Have or had liver problems: you may need a lower dose of atomoxetine
- Have high blood pressure: atomoxetine may increase blood pressure
- Have problems with your heart or an irregular heart beat: atomoxetine can increase heart rate (pulse)
- Have low blood pressure: atomoxetine can cause dizziness or fainting in people with low blood pressure
- Are trying to become pregnant, are already pregnant, or are breast feeding
- Have a problem with depression or suicidal thinking

The FDA advised that pediatric patients being treated with atomoxetine should be closely observed for clinical worsening, as well as agitation, irritability, suicidal thinking and unusual changes in behavior, particularly during the initial few months of a course of drug therapy, or at times of dose changes (either increases or decreases). A similar analysis in adult patients treated with atomoxetine for either ADHD or major depressive disorder found no increased risk of suicidal ideation or behavior with use of atomoxetine. In the Public Advisors, the FDA also noted that atomoxetine was approved in 2002 and had been used in more than 2 million patients. Atomoxetine has now been used in 3.4 million people.

The concern expressed about suicidal ideation and atomoxetine is justifiable; however, some caution is required due to the limited number of patients reported with suicidal ideation. Studies concerning the frequency of suicidal ideation in community samples found that thoughts of self injury are quite common in childhood and adolescence. Further studies are required to justify the need to warn the public since these premature warnings may increase the mistrust towards psychoactive medication. Suicidal thoughts found in Strattera study samples (0.37%) in the treated group cannot be considered common.

#### FDA warnings for atomoxetine

The FDA warns the public in their patient information sheet of atomoxetine. Suicidal thoughts were recently added to the list of common side effects of atomoxetine. These also include an upset stomach, decreased appetite, nausea or vomiting, dizziness, tiredness and mood swings in children. Common side effects that may occur with atomoxetine in adults were listed as constipation, dry mouth, nausea, decreased appetite, dizziness, problems sleeping, sexual side effects, problems urinating and menstrual cramps. The FDA prepared a list of additional warning under the heading *What should I tell my healthcare professional before taking Strattera* and listed the following warnings:

The FDA also added another warning for patients on monoamine oxidase (MAO) inhibitors. Patients are warned not to take atomoxetine for at least 2 weeks after stopping taking a MAO inhibitor. People with the eye disease narrow angle glaucoma, are also warned that they should not take atomoxetine.

#### The question of liver damage & atomoxetine

The Strattera product monograph text included a warning concerning its hepatic effects, entitled *Severe liver injury*. The text was not clear concerning the nature of this injury. The text reads: 'Post-marketing reports indicate that Strattera (atomoxetine hydrochloride) can cause severe liver injury in rare cases'. The monograph also stated: 'Although no evidence of liver injury was detected in clinical trials, there have been 2 reported cases of markedly elevated hepatic enzymes and bilirubin, in the absence of other obvious explanatory factors, out of more than 2 million patients during the first 2 years of postmarketing experience'. In one patient, liver injury manifested by elevated hepatic enzymes (up to 40 × upper limit of normal [ULN]) and jaundice (bilirubin up to 12 × ULN), recurred upon rechallenge and was followed by recovery upon drug discontinuation providing evidence that strattera caused the liver injury. Such reactions may occur several months after therapy is started; however, laboratory abnormalities may continue to worsen for several weeks after the drug is stopped. Due to probable under-reporting, it is impossible to provide an accurate estimate of the true incidence of these events. The patients described above recovered from their liver injury and did not require a liver transplant. However, in a small percentage of patients, severe drug-related liver injury may

progress to acute liver failure resulting in death or the need for a liver transplant. Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted. Laboratory testing to determine liver enzyme levels should be performed upon the first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness or unexplained flu-like symptoms). From a clinical perspective, this warning appears to be reasonable. With the given explanation of the two cases leading to this warning, the diagnosis of 'acute, transitional toxic hepatitis' rather than 'severe liver injury' would be better. However, before full examination of all the information, it would not be possible to predict the nature of the liver problem for these patients. In the process of sharing information concerning atomoxetine side effects, this liver problem, as occurred in these two patients, should be mentioned and documented in the file. The report of these two cases may not justify liver function test monitoring for healthy patients. It must be stated here that atomoxetine has been administered to 3.4 million people and one probable and one possible case of hepatotoxicity should not be considered as a common side effect. The FDA is reviewing all treatments for ADHD including psychostimulants for psychiatric side effects.

#### **Expert commentary**

Atomoxetine has been a significant treatment alternative to psychostimulants in the treatment of ADHD, particularly in the following areas.

#### ***Better control of early morning behavior problems***

One of the most significant characteristics of atomoxetine in ADHD treatment is its long duration of effect. The presence of a long duration of effect of approximately 24 h fits the current conceptualization of ADHD as a disorder that affects the patient across the entire day. Some patients with ADHD have serious problems in settling at bedtime and experience sleep difficulties. ADHD is not a disorder limited to school hours. Many patients with ADHD begin to experience difficulties as soon as they wake up. Early morning, particularly during the week days, is often reported as being a 'rush hour' for the entire family. Psychostimulants require time to reach maximum effects. Until the maximum medication control has been reached, the child with ADHD combined type

or hyperactive/impulsive type and especially children with ADHD and oppositional defiant disorder and/or conduct disorder may have severe behavioral problems at home. After the dose adjustment is completed, atomoxetine regulates early morning behavior with sufficient blood levels of stable medication, prior to the administration of the first daily dose.

#### ***Better control of evening & bedtime problems***

Many ADHD children present behavioral difficulties after school. Behavior problems are often present at dinner time or after the time when homework is completed. Ongoing hyperactivity, loudness and disruptiveness of children with ADHD continue to be a problem between dinner and bedtimes. Some children with ADHD experience great difficulty in going to sleep and often create disruptions in the schedules/routines of other family members. The longest acting psychostimulants (Adderall XR® or Concerta®) have approximately a 12-h duration of effect. Children who take their medication in the morning (~7:00 am) may not have sufficient medication control from the evening meal through to bedtime. Some physicians add a shorter acting amphetamine such as dextroamphetamine (Dexedrine®) and methylphenidate (Ritalin®) to help improve behavioral symptoms in the evening; however, in most cases late use of psychostimulants may suppress sleep. Many patients on psychostimulants do not benefit from the positive effects of the medication in the evenings. Older children, adolescents and adults who require improved attention to do homework in the evenings and/or have positive social/work performance, may not benefit from psychostimulant medications due to sleep suppression. This is an important advantage in the use of atomoxetine in the treatment of ADHD over other psychostimulants.

#### ***Clinical guidelines in medication selection in the treatment of ADHD***

Until the approval of atomoxetine by the FDA, psychostimulants were the only approved medications for ADHD treatment. With the formal approval of atomoxetine by the FDA and regulatory bodies in other parts of the world, a debate was started regarding which medications should be considered as first-line treatment agents. The three main approaches to this question were identified:

- Psychostimulants as the first-line medication
- Atomoxetine as the first-line medication
- Both medications as first-line drugs (individually considering medication choices based on the characteristic profiles of each patient; i.e. a case-by-case approach)

The author of this paper supports the view that the two groups of medications approved as ADHD treatment agents cannot be selected one over the other as the effect size of these medications are relatively similar. There seem to be differences in the desired effects and side effect profiles. The selection process cannot be overly simplified and generalized to all ADHD patients, regardless of their comorbidity and symptom profiles and differing requirements in terms of duration of effect. The following dimensions are listed as possible clinical guidelines in determining which medications should be considered first. This is a complicated clinical process requiring in-depth knowledge concerning the characteristics of the medications and individual differences in patient profiles.

The process of matching these characteristics and finding the best fit between the medication and the patient is a complex and thorough one. The following clinical guidelines may be useful in the selection of the most appropriate medication for each patient.

#### *Earlier response to ADHD medications*

The presence of a good response, nonresponse or insufficient response to one type of medication will provide a clinically useful guide in future medication selection. Patients who have sufficiently responded to one type of medication with little or no side effects should be given the medications to avoid going through unnecessary trials. Patients who did not demonstrate sufficient responses to a good enough trial should be given a different medication from a different class. In the determination of sufficient response, the new concepts of normalization or remission should be taken into consideration. In the past, when the clinician saw a drop of approximately 50% in rating scales, they considered the medication to have achieved the desired effect. The patients who have ADHD symptoms throughout the day, late evening and bedtime may benefit from atomoxetine rather than psychostimulants due to the longer duration of effect of this medication. Patients who need almost immediate medication response due to the presence of serious noncompliant and/or aggressive behaviors may not wait

for the slower dose adjustment of atomoxetine. In some cases it may take a month to titrate to full dose and the effect size of the difference between placebo and active drug is increasing at 9 weeks [63]. The patients and families need to be prepared for this. Further studies are needed to determine more clearly at what point the drug typically achieves optimal effects. The clinicians who are well informed concerning the safety of the combined use psychostimulants with the newer generation antipsychotics such as risperidone (Risperdal®) may prefer starting these patients with psychostimulants with a fast dose escalation and may not want to take risks for negative outcomes by selecting medications like Strattera or TCAs that require longer dose adjustment and response time.

#### *Side effect profiles for previous medications*

A careful history of the patients' variety and severity of side effects, changes with the continuation of treatment or dose adjustment, and their response to different strategies should be recorded to determine the best medication with minor or no side effects. The negative impact of the side effects on the patient and their overall functioning should be carefully compared when determining the medication.

#### *Obtainability & affordability of the medication*

The newer generation ADHD medications are two to three times more expensive than the older short-acting medications. Some of the new-generation ADHD medications are not covered by third party payers and government drug plans. Families who are not able to afford these drugs may need the most effective use of the medications that are reimbursed for them or the medications they can afford. This should be openly reviewed by the physician with the family. The economic burden created by certain medications may play an important role in the continuation of the treatment or early termination.

#### *Response of the selected medication in associated problems &/or comorbid disorders*

It has been well established that most patients with ADHD are comorbid for other disorders and many suffer from serious problems impairing their day-to-day functions, such as sleep and social behaviors. Patients presenting with sleep initiation and maintenance problems may respond better to atomoxetine rather than psychostimulants. Atomoxetine can be considered for patients with ADHD and comorbid

tic disorders and anxiety disorders as there is evidence that these disorders respond more favorably to atomoxetine rather than psychostimulants. The most common comorbid disorders include oppositional defiant disorder, conduct disorder, mood disorders and anxiety and tic disorders [14,77,78]. Stimulant medications may exacerbate some of the symptoms of anxiety and depression and may also aggravate tics in other patients. Over 50% of patients with Tourette disorder or pervasive developmental disorder also suffer from ADHD symptoms. Two recent studies on Tourette's syndrome and ADHD reported that these two disorders commonly overlap [79,80]. These studies indicate that comorbidities are the rule rather than the exception in ADHD. Atomoxetine, with reported positive effect on tics, enuresis, anxiety disorders and symptoms as well as depressive symptoms may be a good treatment alternative in ADHD alone and in the multiple comorbidities associated with ADHD.

### *Patient, family & physician biases towards some medications*

The biases of patients and families may play an important role in the acceptance of medication treatment and compliance. If all comparisons concerning the medications are similar, patient and family preferences regarding the choice of the medication should be taken into account. Patients and families who are comfortable with the medication may be more compliant.

### *Lack of high risk for aversion & abuse*

Although it has been well documented that the treatment of ADHD with psychostimulants may reduce the risk of substance abuse, there are still some patients who may abuse psychostimulants. Earlier substance abuse and/or a history of substance abuse in the family may lead to considering atomoxetine rather than psychostimulants as the abuse potential for atomoxetine is lower than with psychostimulants.

### **Outlook**

The initial research studies with atomoxetine focused on the determination of this medication as a viable treatment alternative for ADHD. More recent abstracts published in international meetings are encouraging the use of atomoxetine in multiple, complex disorders with ADHD. The studies demonstrate the safe and effective use of the combined treatments with both atomoxetine and psychostimulants and

will significantly contribute to the improved treatment of ADHD patients, particularly those who suffer from multiple disorder and ADHD. This combination may improve the weaknesses of both medications, as psychostimulants may speed up the treatment response, while atomoxetine may help in improving behavior in the evenings and reversing the sleep suppression created or exacerbated by psychostimulants. It may be hypothesized that the combined use will provide better treatment response and higher effect sizes in clinical studies.

As atomoxetine appears to have antianxiety and anti-tic features as well as a positive effect in treating depressive symptoms associated with ADHD, it can be expected that we will see many published studies concerning the multiple effects of atomoxetine.

It may be predicted that studies reviewing the role of atomoxetine in children with enuresis nocturna will be increased in the next 5 years. Enuresis nocturna has been found more commonly in ADHD patients [14,77,78]. The comparison of the positive effects and side effect profile of atomoxetine with other commonly used treatment options (i.e, inhalers or imipramine) may shed new light in this area of clinical research. As atomoxetine has a better side effect profile than imipramine, the role of this medication in the treatment of enuresis nocturna may provide an improved acceptance and compliance by patients and families.

The measurability of plasma levels and improvements reported in the use of blood levels to increase the response for fast metabolizing patients, may give a better treatment response rate and a better effect size by increasing the differences between the medication versus placebo response. Patients with regular response may not require monitoring with plasma levels of atomoxetine. The use of plasma levels in patients not responding well to the maximum doses of atomoxetine may need treatment with plasma levels to improve their response. The combined use of atomoxetine with other psychoactive medications, including those that use the CYP2D6 system, may also benefit from atomoxetine plasma level monitoring to ensure safe treatment with maximum benefits. This represents a burgeoning new field for research.

It is expected that future studies will also include the effective and safe treatment of ADHD patients with serious oppositional defiant behavior associated with aggression and



other symptoms of conduct disorder. The efficacy and safety of psychostimulant–risperidone combination has been studied and used effectively in treating seriously aggressive patients [80–86]. Atomoxetine use with antipsychotics may be tested in a few research studies. Aggressive behavior is not limited to school time. Long duration of effect of atomoxetine may provide a better combination treatment with risperidone or other new generation antipsychotics with strong antiaggressive features. After the establishment of safety and efficacy of atomoxetine–antipsychotic combinations, these combinations can be compared with psychostimulant–antipsychotic medication combinations to maximize the benefits and minimize the side effects. The studies dealing with safety of patients and the people around them by

controlling aggressive, conduct disordered patients with atomoxetine or other medications combined with atomoxetine, will increase the growing respect for this new medication.

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### Highlights

- Atomoxetine can be accepted as one of the first-line medications for attention deficit/hyperactivity disorder (ADHD), specifically for patients who require longer than 12 h of symptom control.
- The addition of atomoxetine to existing treatment options has improved the capacity to effectively treat ADHD and its comorbid disorders.
- Patients with ADHD who require faster than 4 to 8 weeks treatment response may be served better with psychostimulants.
- Atomoxetine and psychostimulants complement each other and their combined use in the future may improve treatment response.
- Objectives, sample size and sample selection, methodology and measurement instruments in studies reporting and interpretation of the results and conclusions meet the expectations of international standards for medication studies.
- The future use of atomoxetine as an alternative to stimulants may become very beneficial for patients who suffer from ADHD.
- It is hypothesized that atomoxetine may be effective in medication-naïve patients and also stimulant-resistant patients and/or be an effective alternative for those who experience negative side effects with stimulant medications.
- It is likely that atomoxetine will be a safe and effective alternative for ADHD patients with tic disorders, mood and/or anxiety disorders.
- Some of the positive features of atomoxetine that make it a good alternative to psychostimulant medications are;
  - Continuous symptom relief for 24 h with one dose of medication at home and school
  - Improved measurements of functional outcome
  - Antianxiety and anti-tic features
  - Incidence of insomnia is comparable to placebo
  - Reduced risk of substance abuse
  - Extended safety data to 4 years
  - Ease of dosing

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