Chapter 1

Evidence-based pharmacotherapy of attention deficit hyperactivity disorder

Brigette S. Vaughan, John S. March, and Christopher J. Kratochvil

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurobiological disorder, affecting significant numbers of children, adolescents, and adults worldwide. Research throughout the past century has established a strong scientific foundation for our current understanding of the etiology, epidemiology, and treatment of ADHD. The American Medical Association's Council on Scientific Affairs in 1998 stated, "Overall, ADHD is one of the best-researched disorders in medicine, and the overall data on its validity are far more compelling than for many medical conditions" (Goldman *et al.*, 1998). The American Academy of Child & Adolescent Psychiatry (AACAP), in their 2007 ADHD Practice Parameters concluded, "Although scientists and clinicians debate the best way to diagnose and treat ADHD, there is no debate among competent and well-informed healthcare professionals that ADHD is a valid neurobiological condition that causes significant impairment in those whom it afflicts" (Pliszka, 2007).

Neuropsychological, neuroimaging, and genetic studies have demonstrated the biological underpinnings of ADHD. These studies have correlated deficits in executive functioning, response inhibition, delay aversion, vigilance, working memory, and planning with specific regions of the brain (Willcutt *et al.*, 2005). Structural imaging studies have demonstrated that children with ADHD have significantly smaller brain volumes, on average, than same-aged comparison children (Castellanos & Tannock, 2002; Durston *et al.*, 2004; Mostofsky *et al.*, 2002), with smaller cerebellar and total cerebral volumes noted (Castellanos *et al.*, 2002). In addition, functional imaging has revealed discrete variations in brain activation, specifically in the frontal-striatal cerebellar circuits (Krain & Castellanos, 2006). Family, twin, and more recently, genotyping studies provide further support for the biological basis of ADHD. There is considerable evidence that the principal cause of ADHD is genetic, with an estimated heritability of 76% (Faraone *et al.*, 2005). Parents of children with ADHD are 2–8 times more likely to have the disorder themselves, and the risk is similar for siblings of affected children (Faraone & Biederman, 2000).

ADHD has been conservatively estimated to occur in 3–7% of children (APA, 2000), with other estimates as high as 7–12% (CDC, 2005; Woodruff *et al.*, 2004). While most commonly

Essential Evidence-Based Psychopharmacology, Second Edition, ed. Dan J. Stein, Bernard Lerer, and Stephen M. Stahl. Published by Cambridge University Press.

diagnosed between ages 7 and 10 years, symptom presentation and impairment can often be seen in children as young as age 3 years (Lavigne *et al.*, 1996). Epidemiological studies have shown that 2–6% of preschool children meet diagnostic criteria for ADHD (Angold *et al.*, 2000; Lavigne *et al.*, 1996). Of those diagnosed with ADHD as children, 60–85% continue to meet criteria for the disorder as adolescents, and as many as 60% continue to experience symptoms as adults (Barkley *et al.*, 1990, 2002; Biederman *et al.*, 1996; Kessler *et al.*, 2005).

A comprehensive differential diagnosis is essential for an accurate evaluation. Behaviors which are characteristic of normal childhood development may be misinterpreted as ADHD if not considered in an age-appropriate context. In addition, developmental disabilities, learning disorders, mental retardation, and hearing or vision impairments, as well as general medical problems such as hyperthyroidism, partial complex seizures, or lead toxicity may mimic ADHD. Several aspects of the core symptoms of inattention, hyperactivity, and impulsivity, can also be indicative of depressive and anxiety disorders, substance abuse, or pediatric bipolar disorder.

The diagnostic criteria for ADHD require the presence of at least 6/9 inattentive symptoms, and/or 6/9 hyperactive-impulsive symptoms, with onset prior to age 7 years. Symptoms must be developmentally inappropriate and result in clinically significant impairment in social, academic, and/or occupational functioning (APA, 2000). Even preschool children with ADHD are at high risk for academic, social, behavioral, and family dysfunction due to the disorder (DuPaul *et al.*, 2001), and are more likely to be placed in specialized educational settings (Lahey *et al.*, 1998, 2004). These children also have increased rates of accidents and injuries (Lahey *et al.*, 1998), aggression (Connor *et al.*, 2003), and internalizing symptoms (Cunningham & Boyle, 2002). School-aged children with ADHD as a group have more difficulties with peer interactions, academic tasks, and conflicts with parents than do same-aged peers without ADHD. In addition to ongoing difficulties common to younger children, adolescents have elevated rates of substance use and abuse, motor vehicle accidents, academic and occupational impairments, teen pregnancy, and sexually transmitted diseases (Barkley, 2006).

Nearly two-thirds of children diagnosed with ADHD also have at least one co-occurring psychiatric condition. The Multimodal Treatment Study of Children with ADHD (MTA) consisted of one of the largest and best characterized ADHD populations to date ($n = 579$ children aged 7–9.9 years), and demonstrated that only 31% of participants had ADHD alone, while 40% also met criteria for oppositional defiant disorder, 38% for anxiety/mood disorders, 14% for conduct disorder, and 11% for tic disorders (MTA Cooperative Group, 1999).

The National Initiative for Children's Healthcare Quality (NICHQ) recommends that children with ADHD and their families receive individualized treatment with ongoing support and education (Bodenheimer *et al.*, 2002*a*, 2002*b*). They recommend that an effective ADHD management plan for children should generally include parent training, behavioral modification and social-skills training, and school-based interventions. In preschool children, or those with mild symptoms, the AACAP (Pliszka, 2007) and American Academy of Pediatrics (AAP, 2001) recommend a trial of behavioral interventions prior to starting medication. Unfortunately, studies have shown that while behavioral therapies offer some benefit, they may have limited effectiveness as a monotherapy for treating moderate to severe ADHD. In the majority of cases, behavioral interventions may be only one component of a more extensive treatment plan.

Table 1.1. Treatment recommendations from the AACAP Practice Parameters for the assessment and treatment of attention deficit hyperactivity disorder (Pliszka, 2007).

Treatment	Monitoring
• The treatment plan for the patient with ADHD should be well thought out and comprehensive.	• Patients receiving pharmacotherapy for ADHD should have their height and weight monitored throughout treatment.
• Pharmacological treatment should begin with an agent approved by the FDA for the treatment of ADHD.	• The patient should be monitored for treatment-emergent side-effects during pharmacotherapy.
• If a patient responds robustly to pharmacotherapy, medication treatment of their ADHD alone may be sufficient.	• If a patient has a suboptimal response to medication, a comorbid diagnosis, or psychosocial stressors, adjunctive psychosocial intervention is often beneficial.
• If none of the FDA-approved medications result in satisfactory treatment, the clinician should review the diagnosis and consider behavioral therapy and/or the use of medications not approved by the FDA for the treatment of ADHD.	• Treatment should continue as long as symptoms remain present and cause impairment. The need for treatment should be periodically reassessed.

The MTA study randomized participants to intensive behavioral therapy, pharmacotherapy with systematically delivered methylphenidate, a combination of the two, or standard community care. The pharmacotherapy and combined treatment groups demonstrated significant improvement, and both were superior to behavioral therapy alone. Interestingly, however, the combined treatment group's response was not significantly better than pharmacotherapy alone for the treatment of core ADHD symptoms. Medication, therefore, appears to have the most significant acute impact on the treatment of ADHD (MTA Cooperative Group, 1999). The addition of behavioral interventions to pharmacotherapy did, however, increase parent and teacher satisfaction with treatment, improved children's interpersonal relationships, and on average, children receiving behavioral interventions required lower medication doses (MTA Cooperative Group, 1999). A later study of children aged 3–5.5 years with moderate to severe ADHD, the Preschool ADHD Treatment Study (PATS), demonstrated limited response to behavioral therapy alone, resulting in the majority of children warranting the initiation of pharmacotherapy following treatment with only behavioral intervention (Greenhill *et al*., 2006).

Practice parameters

The AACAP Practice Parameters for ADHD published in 2007 combine short- and long-term empirical evidence with expert opinion from pediatric mental health researchers and clinicians. They offer specific recommendations (Table 1.1) for a comprehensive treatment plan, potentially consisting of pharmacological and behavioral interventions, and that if pharmacotherapy is indicated, the initial agent selected should be one with US Food and Drug Administration (FDA) approval for ADHD. The AACAP further states that if the response to an FDA-approved treatment is robust and normalizes the patient's functioning, medication alone may be sufficient (Pliszka, 2007).

In their 2001 clinical practice guideline for treating ADHD in children, the AAP recommended that the first intervention for the young child with ADHD be behavioral (AAP, 2001).

Table 1.2. Treatment algorithm for preschool children with attention deficit hyperactivity disorder (Gleason *et al.*, 2007).

General principles
• Assessment and diagnosis should be comprehensive, developmentally appropriate and contextually sensitive. • An adequate trial of psychotherapy should precede pharmacotherapy, and should continue even if medication is used. • Pharmacotherapy should be considered in the context of the clinical diagnosis and degree of functional impairment. • Referral of the parent for treatment may optimize family mental health. • Medication discontinuation trials are recommended following 6 months of treatment. • The use of additional medication to manage side-effects of medication is discouraged.

Stage 0: Diagnostic assessment and psychotherapeutic intervention.
Stage 1: Methylphenidate trial.
Stage 2: Amphetamine trial.
Stage 3: a-adrenergic or atomoxetine trial.

The 2007 AACAP (Pliszka, 2007) parameters indicate that behavioral therapy alone may be appropriate in mild cases of ADHD and should be considered for young children. Additionally, Gleason and colleagues made specific recommendations regarding treatment algorithms for pharmacotherapy in preschool-aged children (Table 1.2) (Gleason *et al.*, 2007). Gleason and colleagues went on to specifically address treatment of preschool-aged patients with ADHD and referenced the PATS study when providing guidance for treating young children with a psychostimulant. The AACAP does note that subjects in PATS were only randomized to pharmacotherapy if they did not demonstrate significant or satisfactory improvement following 10 weeks of parent training (Greenhill *et al.*, 2006).

What is the first-line treatment for ADHD?

The role of pharmacotherapy (Table 1.3) as a first-line treatment of ADHD is strongly supported in the literature (Biederman & Spencer, 2008). The stimulant medications have decades of efficacy data from hundreds of controlled trials, beginning as early as the 1930s, and were well-established as effective treatments for ADHD by the 1970s. The pediatric safety and efficacy database on acute and long-term use of these agents has continued to grow and includes data not only on school-aged children, but more recently has expanded into preschool children and adolescents (AAP, 2001; Biederman & Spencer, 2008; Brown *et al.*, 2005; Greenhill *et al.*, 2002; Pliszka *et al.*, 2007). There has also been a significant increase in data supporting the utility of non-stimulant agents for ADHD in the past 10 years (AAP, 2001; Biederman & Spencer, 2008; Brown *et al.*, 2005; Greenhill *et al.*, 2002; Madaan *et al.*, 2006; Pliszka *et al.*, 2007). A meta-analysis of atomoxetine and stimulant studies revealed a robust effect size for atomoxetine and the stimulants, both of which are currently approved by the FDA for the treatment of ADHD. Atomoxetine demonstrated an effect size of 0.62, which would be considered a medium effect size, compared with 0.91 and 0.95, considered large effect sizes, for immediate- and extended-release stimulants, respectively (Faraone, 2003). A more recent FDA-approved agent, the a_2 agonist guanfacine XR, demonstrated effect sizes of 0.43–0.86 in two double-blind, placebo-controlled (DBPC) trials (Biederman *et al.*, 2008*b*; Sallee *et al.*, 2009*b*).

Table 1.3. Medications with FDA approval for the treatment of attention deficit hyperactivity disorder.

Name	Delivery system	Duration of effect (Daughton & Kratochvil, 2009)	Trade name
Methylphenidate	Solution	4 h	Methylin
	Chewable tablet	4 h	Methylin
	Tablet	4 h	Ritalin
	Sustained release tablet	Up to 8 h	Ritalin SR
	Beaded capsule	7–8 h	Metadate ER, Methylin ER, Ritalin LA
	Beaded capsule	8–9 h	Metadate CD
	OROS capsule	Up to 12 h	Concerta
	Transdermal patch	12 h	Daytrana
d-Methylphenidate	Tablet	4 h	Focalin
	Beaded capsule	Up to 12 h	Focalin XR
Amphetamine	Tablet	6 h	Adderall
	Beaded capsule	10 h	Adderall XR
d-Amphetamine	Tablet	4 h	Dexedrine, Dextrostat
	Spansule capsule	10 h	Dexedrine Spansule
Lisdexamfetamine	Capsule	10 h	Vyvanse
Atomoxetine	Capsule	24 h	Strattera
Guanfacine extended-release	Tablet	8–12 h	Intuniv
Clonidine extended-release	Tablet	12 h	Kapvay

Stimulants

Stimulants have historically been considered a first-line treatment for ADHD, with approximately 75% of children responding to the first agent selected, and 80–90% eventually responding if two different stimulants are tried consecutively (Pliszka, 2003). Although the MTA study examined the use of immediate-release methylphenidate, extended-release preparations are now commonly used to improve adherence to the treatment schedule, thus providing less opportunity for gaps in coverage. A combination of immediate- and extended-release preparations, selected and titrated according to tolerability and response, may ultimately be required to optimally manage the child's individual pharmacotherapy needs. All stimulant medications currently approved for the treatment of ADHD are derivatives of either methylphenidate or amphetamine, both of which act by enhancing the neurotransmission of dopamine, and to a lesser extent, norepinephrine (Biederman & Spencer, 2008). DBPC studies in children, adolescents, and adults have demonstrated that 65–75% of subjects typically respond to stimulant treatment, compared with 4–30% of those on placebo (Greenhill *et al.*, 2002; Pliszka, 2007). Recent research has focused on improving the delivery mechanisms of the stimulant medications in order to extend the duration of action. With multiple formulations of these medications (short-, intermediate-, and long-acting) as well as a variety of administration options available (e.g. capsules, sprinkleable capsules, tablets, chewable tablets, oral solution, transdermal patches), treatment can be tailored to individual patient needs.

The MTA study demonstrated the tolerability and efficacy of t.i.d. immediate-release methylphenidate in a randomized trial of 579 children aged 7–9.9 years with the combined subtype of ADHD. Dose titration was based on effect as reported by parent and teacher rating scales, and tolerability. Children in the manualized pharmacotherapy arm of the study had mean final doses of 32.1 ± 15.4 mg/day, and those assigned to manualized pharmacotherapy plus behavioral intervention had mean final doses of 28.9 ± 13.7 mg/day. The MTA study allowed children weighing <25 kg to have methylphenidate doses of up to 35 mg/day, and allowed doses up to 50 mg/day for children who weighed more. Average doses in the smaller children were 0.95 ± 0.40 mg/kg, and 1.13 ± 0.55 mg/kg in those that were heavier (MTA Cooperative Group, 1999).

Prior to the NIMH-funded PATS there were fewer than a dozen small placebo-controlled trials of psychostimulants in preschool children, and all utilized immediate-release methylphenidate (Kratochvil *et al.*, 2004). Doses in these studies did not exceed 0.6 mg/kg, a narrower range than the 0.3–1.0 mg/kg used in older children (Kratochvil *et al.*, 2004), and were administered q.i.d. or b.i.d., rather than the t.i.d. schedule often required for optimal effect. Efficacy of methylphenidate in the preschool age group varies from older children (Connor, 2002), as does the adverse effect profile (Firestone *et al.*, 1998). PATS, which used a titration model similar to the MTA's, included 165 children aged 3.5–5 years initially randomized to either placebo or immediate-release methylphenidate (1.25 mg, 2.5 mg, 5 mg, or 7.5 mg t.i.d.). Subjects received a week of treatment with each dose during the double-blind cross-over titration phase. Twenty-two percent of subjects were identified as best responding to 7.5 mg t.i.d. The mean final best dose in PATS was 14.22 ± 8.1 mg/day, or 0.7 ± 0.4 mg/kg.day (Greenhill *et al.*, 2006).

When PATS data were compared with MTA data, it was noted that the younger children had lower optimal doses, by weight, of immediate-release methylphenidate (0.7 mg/kg.day compared with 1.0 mg/kg.day). Pharmacokinetic data also demonstrated a slower clearance of a single dose of methylphenidate in 4- and 5-year-old children compared with school-aged children (Wigal *et al.*, 2007). Tolerability seems to have age-related variability, with younger children demonstrating more emotional adverse events (e.g. crabbiness, irritability, and proneness to crying) than school-aged children. Thus, slower titration, closer monitoring and smaller doses of stimulants are advised when treating preschool children (Pliszka, 2007).

Adverse effects

All formulations of the stimulant medications have similar adverse-event profiles (Greenhill *et al.*, 2002). Delayed sleep-onset, decreased appetite, weight loss, headache, stomach upset and increased heart rate and blood pressure are common. Emotional outbursts and irritability have also been frequently reported in younger children (Wigal *et al.*, 2006).

Concerns with cardiovascular safety of ADHD pharmacotherapies have led to specific recommendations for pre-treatment evaluation, treatment selection, and monitoring. Much scrutiny is given to the risks present for children with structural cardiac abnormalities, but potentially medication-related changes in heart rate and blood pressure are also observed in healthy children with ADHD. In a study of 10 years of Florida Medicaid claims, stimulant use in patients with ADHD was associated with 20% more emergency-room visits, and 21% more office visits for cardiac symptoms (Winterstein *et al.*, 2007).

Gould *et al.* (2009) reported that the rate of sudden death in pediatric patients taking a psychostimulant was the same as that seen in the general population, with 11 sudden deaths

reported between 1992 and 2005. However, in a matched case-control study, a significant association of stimulant use with sudden death was seen when comparing data for 564 reports of sudden death in 7- to 19-year-olds with the deaths of 564 same-aged patients who died in motor vehicle accidents (odds ratio 7.4, 95% confidence interval (CI) 1.4–74.9) (Gould *et al.*, 2009).

The AAP (Perrin *et al.*, 2008) recommends that a targeted cardiac history and physical examination be part of the assessment of a child prior to initiating ADHD treatment. Questions regarding a prior patient history of heart disease, palpitations, syncope or seizures, or a family history of sudden death in children or young adults, cardiomyopathy or long-QT syndrome should be asked. If these are present, an ECG and/or referral to a cardiologist may be warranted prior to initiating treatment. These cardiovascular risks may become more of an issue in the treatment of adults who may have concurrent hypertension and/or cardiovascular disease.

Atomoxetine

Atomoxetine, which selectively blocks re-uptake at the noradrenergic neuron, was the first non-stimulant medication approved by the FDA for the treatment of ADHD. Two large, DBPC efficacy studies demonstrated significant improvement in ADHD symptoms with atomoxetine compared with placebo, with 64.1% and 58.7% of atomoxetine subjects responding (Spencer *et al.*, 2002). More than a dozen DBPC trials have provided evidence supporting the safety and efficacy of atomoxetine dosed both once- and twice-daily for the treatment of ADHD in children, adolescents, and adults (Kelsey *et al.*, 2004; Michelson *et al.*, 2001, 2002, 2003; Spencer *et al.*, 2002; Weiss *et al.*, 2005).

The FDA-approved target therapeutic dose of 1.2 mg/kg.day was selected following a dose-finding study which observed a graded dose-response to atomoxetine 0.5 mg/kg.day and 1.2 mg/kg.day, but no significant difference between 1.2 mg/kg.day and 1.8 mg/kg.day for reduction of core ADHD symptoms. Improvements in psychosocial functioning, however, were seen when the dose was increased to 1.8 mg/kg.day without any significant difference in adverse events (Michelson *et al.*, 2001).

Atomoxetine is not approved for use in children aged < 6 years. However, there has been one DBPC trial ($n = 101$), examining the use of atomoxetine in 5- and 6-year-olds. Improvements were noted on parent and teacher ADHD–IV ratings for children assigned to atomoxetine compared with those on placebo ($p < 0.05$). Three subjects withdrew from the study due to adverse events (atomoxetine = 0, placebo = 3). The mean final daily dose of atomoxetine was 1.38 mg/kg.day. Despite statistically significant improvements in ADHD symptoms, and the fact that the parents received concomitant education on ADHD and behavioral interventions as a part of the study, the children continued to have ADHD–IV (parent) scores above the 86th percentile for age and gender at study completion (Kratochvil *et al.*, 2008*b*).

Adverse effects

Common acute adverse effects of atomoxetine include sedation, loss of appetite, nausea, vomiting, irritability, and headaches. In an analysis of the efficacy and tolerability of atomoxetine in young *vs.* older children, no significant differences were noted in the adverse event profile or response to atomoxetine (Kratochvil *et al.*, 2008*a*).

Atomoxetine carries additional warnings for hepatotoxicity and suicidality risk. An analysis of laboratory data from 7961 adult and pediatric subjects in atomoxetine clinical

trials revealed 41 instances of elevations in AST and ALT. There were 351 spontaneous reports of hepatic events in the first 4 years atomoxetine was on the market. Of these, three suggested atomoxetine as a probable cause, and 1/3 had a positive re-challenge. In all three cases, symptoms resolved following discontinuation of atomoxetine. These data resulted in recommendation that atomoxetine be discontinued if jaundice or elevations in hepatic enzymes are present (Bangs *et al.*, 2008*a*). A 2008 analysis of data from 14 studies of atomoxetine by Bangs and colleagues demonstrated that suicide ideation was more common in subjects receiving atomoxetine (0.37%, 5/1357 subjects) compared with those receiving placebo (0%, 0/851 subjects). To place the risk of suicidality in context, the number needed to harm (NNH) was 227, whereas the number needed to treat (NNT) to achieve remission of ADHD symptoms was five. No suicides occurred in any of the trials in the analysis (Bangs *et al.*, 2008*b*).

Stimulant and atomoxetine comparator trials

Atomoxetine and osmotic release oral system (OROS) methylphenidate

In a comparator trial in 516 children and adolescents aged 6–16 with ADHD, subjects were randomized to 6 weeks of treatment with either atomoxetine up to 1.8 mg/kg.day ($n = 222$), OROS methylphenidate up to 54 mg/day ($n = 220$) or placebo ($n = 74$). Atomoxetine and OROS methylphenidate were both superior to placebo, with 45% ($p < 0.003$) and 56% ($p < 0.001$) responding, respectively. Effect sizes were 0.6 for atomoxetine and 0.8 for OROS methylphenidate. Decreased appetite was the only adverse event separating from placebo for both active treatments ($p < 0.05$). Subjects receiving OROS methylphenidate reported experiencing insomnia, while those assigned to atomoxetine had more frequent complaints of somnolence. Weight loss and increased diastolic blood pressure ($p < 0.05$) were noted to be significant for both drugs compared with placebo, and an increased pulse rate was significant in the atomoxetine group compared with OROS methylphenidate and placebo ($p < 0.05$) (Newcorn *et al.*, 2008).

For the stimulant-naive patients ($n = 191$) participating in this trial, response rates to atomoxetine (57%, $p = 0.004$) and methylphenidate (64%, $p < 0.001$) were comparable ($p = 0.43$), but those subjects with prior exposure to stimulants ($n = 301$), had better responses to methylphenidate (51%, $p = 0.002$) than to atomoxetine (37%, $p = 0.09$) ($p = 0.03$) (Newcorn *et al.*, 2008). The effect size for atomoxetine was greater in stimulant-naive patients (0.9), compared with patients previously treated with stimulants (0.5), while the effect-sizes for OROS methylphenidate in patients not previously treated with a stimulant and with prior exposure were 1.0 and 0.8, respectively (Newcorn *et al.*, 2008).

Subjects initially assigned to OROS methylphenidate were then switched to atomoxetine at the end of the 6-week acute treatment phase of the study. Forty-two percent (29/69 subjects) who did not respond to atomoxetine in the second phase of the study had previously responded to OROS methylphenidate during acute treatment, while 43% of subjects who did not respond acutely to OROS methylphenidate (30/70 subjects) went on to respond to atomoxetine. This may indicate a differential response to treatment for some patients (Newcorn *et al.*, 2008).

Atomoxetine and mixed-amphetamine salts

In a 3-week laboratory school comparison of atomoxetine and extended-release mixed amphetamine salts in 6- to 12-year-olds with either combined or hyperactive-impulsive

type ADHD, improved attention and academic performance were noted with both treatments. Mixed amphetamine salts-treated subjects had greater improvements than those who received atomoxetine ($p < 0.001$). The difference at end-point was statistically and clinically significant; however, the relatively short 3-week duration of the study may not have been sufficient to demonstrate the full effect of atomoxetine treatment. The mixed amphetamine salts group reported experiencing insomnia, decreased appetite, upper abdominal pain, anorexia and headache, while the most common adverse events reported in the atomoxetine group were somnolence, appetite decrease, upper abdominal pain, vomiting, and headache. Vital sign changes were similar for both groups and were not statistically significant (Wigal *et al.*, 2005).

a_2 agonists

The a_2 adrenergic agents, clonidine (Catapres) and immediate-release guanfacine (Tenex), have been used relatively commonly over the past decade as second-line or adjunctive treatments in the USA. International comparisons (Winterstein *et al.*, 2008), however, show very different co-medication patterns between the USA and European countries where a_2 adrenergic agents are rarely used. Clonidine has been shown to reduce ADHD symptoms in patients with comorbid tics, aggression and conduct disorder. Immediate-release clonidine is short-acting and requires multiple divided doses throughout the day (Brown *et al.*, 2005). In the USA clonidine is also available as a transdermal patch, allowing for once-weekly application. An extended-release formulation (Kapvay™) was approved by the FDA in September 2010, for the treatment of ADHD in children and adolescents aged 6–17 years. Kapvay received approval as both monotherapy and in combination with a stimulant.

Guanfacine is a more selective a_2-adrenergic agonist with less sedation and a longer duration of action (Biederman & Spencer, 2008). A small open-label study of immediate-release guanfacine showed improvements in hyperactivity and inattention, with transient sedation as the most common adverse event (Hunt *et al.*, 1995), and additional studies have demonstrated its utility and good tolerability in treating ADHD with co-occurring tic disorders and Tourette's (Chappell *et al.*, 1995; Scahill *et al.*, 2001). An extended-release form of guanfacine was given FDA approval in 2009 as monotherapy for pediatric ADHD following two controlled trials (study 1: $n = 345$, ages 6–17 years; study 2: $n = 324$, ages 6–17 years). Adverse events were largely dose-dependent. Both studies had similar tolerability data, with the most common treatment-emergent adverse events being headache, somnolence, fatigue, sedation, and upper abdominal pain. No clinically significant vital sign or ECG changes were seen (Biederman *et al.*, 2008*b*; Sallee *et al.*, 2009*b*). Dose-based effect sizes ranged from 0.43 to 0.86, and response rates were 43% for the 3-mg dose and 62% for the 4-mg dose.

Guanfacine's most common acute adverse effects include somnolence, headache, fatigue, upper abdominal pain, and sedation. Bradycardia was reported in long-term studies (Biederman *et al.*, 2008*a*; Sallee *et al.*, 2009*a*).

What is the impact of ADHD pharmacotherapy?

The benefits of pharmacotherapy are most evident in reduction of the core symptoms of ADHD. By reducing inattention, hyperactivity, and impulsivity, patients with ADHD are better able to perform academically and socially. Studies have demonstrated that

children treated with stimulants have improved attention to school work, decreased disruptive behaviors, and decreased non-compliance. Short-term data also show improvements in academic performance and productivity (Barkley, 1998). Some data suggest that children with ADHD treated with psychostimulants demonstrate better academic outcomes as evidenced by WIAT-II subtests and high school grade point average (GPA) than children with ADHD who were not treated. However, the treated children did not do as well as non-ADHD controls. It is unclear if pharmacotherapy alone translates to long-term academic success (Powers *et al.*, 2008).

Social interactions between affected children and their parents, teachers, and peers are significantly improved with stimulant treatment. Treated children are more compliant with commands and more appropriately responsive to interactions with others, with less negative and off-task behavior. As a result, adult redirections and supervision needs decrease, and praise and positive attention to the child increase. ADHD children treated with stimulants also appear to be better accepted by peers, probably as a result of reduced negative and aggressive behavior (Barkley, 1998). Health-related quality-of-life outcomes measured by the Child Health Questionnaire (CHQ) were improved along with ADHD symptoms in children treated with atomoxetine in a DBPC dosimetry study in children and adolescents aged 8–18 years (Michelson *et al.*, 2001).

Early treatment with methylphenidate does not appear to increase risk for negative outcomes, and may have beneficial long-term effects (Mannuzza *et al.*, 2008). However, long-term data from the MTA study notes that benefits of pharmacotherapy are sustainable up to 2 years for the majority of subjects followed, but by the third year of follow-up, only about one third of subjects demonstrated ongoing benefit with medication treatment (Swanson *et al.*, 2008). Despite decreases in ADHD symptoms, the MTA subjects as a group still had relatively poorer ratings of behavior, academic, and overall functioning compared with normal controls at 6- and 8-year follow-ups.

How long should treatment last?

Epidemiological surveys of community samples indicate that 2–6% of preschool children meet diagnostic criteria for ADHD (Angold *et al.*, 2000; Lavigne *et al.*, 1996), with prevalence rates in school-aged children conservatively estimated to be between 3% and 7% (APA, 2000). As children grow into adolescence and adulthood the prevalence of ADHD decreases, yet still persists in significant numbers, estimated at approximately 3–4% in adults (Fayyad *et al.*, 2007). Even though the presentation may vary from early childhood to adulthood, the impairment there is no less significant (Kessler *et al.*, 2006). A multitude of studies have demonstrated a correlation between ADHD in adults and global impairment in functioning, including: smoking and substance abuse, diminished rates of college graduation, occupational/vocational difficulties, motor vehicle accidents, legal problems, unplanned pregnancies, and relationship problems (Barkley, 2006).

In a 10-year case-controlled follow-up study of 112 male adults with ADHD, potential protective factors of stimulant treatment for ADHD were assessed. Biederman *et al.* (2008*c*, 2009) found no evidence that stimulant treatment in childhood or adolescence either increased or decreased the risk for development of substance use disorders in young adulthood, but that ADHD patients treated with stimulants were at significantly less risk of developing depressive and anxiety disorders, disruptive behavior, and repeating a grade in school