ACADEMIC HIGHLIGHTS

Determining and Achieving Therapeutic Targets in Attention-Deficit/Hyperactivity Disorder

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the satellite symposium "Are Therapeutic Targets in ADHD Keeping Pace With Advancements in Treatment?" held December 11, 2002, by the National Academy for the Advancement of ADHD Care.*

The symposium was chaired by ***Joseph Biederman****, M.D., Harvard Medical School and Massachusetts General Hospital, Boston, and McLean Hospital, Belmont, Mass. The faculty were* ***Christopher J. Kratochvil****, M.D., University of Nebraska Medical Center, Omaha;* ***Thomas J. Spencer****, M.D., Harvard Medical School and Massachusetts General Hospital, Boston;* ***Janet Wozniak****, M.D., Harvard Medical School and Massachusetts General Hospital, Boston.*

This ACADEMIC HIGHLIGHTS was independently developed by the Physicians Postgraduate Press, Inc. Office of Continuing Medical Education pursuant to an unrestricted educational grant from Eli Lilly and Company.

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Dr. Biederman *has received research support from Shire Richwood, Eli Lilly, Wyeth, Pfizer, Cephalon, Janssen, Noven, Stanley Foundation, National Institute for Mental Health, National Institute of Child Health and Human Development, and National Institute on Drug Abuse; is a member of the speakers' bureaus of GlaxoSmithKline, Eli Lilly, Pfizer, Wyeth, Shire Richwood, Alza, and Cephalon; and is a member of the advisory boards of Eli Lilly, Celltech, Shire Richwood, Noven, Alza, Ortho-McNeil, and Cephalon;* **Dr. Kratochvil** *is a consultant for and has received honoraria from Eli Lilly; has received research/grant support from Eli Lilly, Ortho-McNeil, and GlaxoSmithKline; and is a member of the speakers'/advisory boards of Eli Lilly, Shire Richwood, and Novartis;* **Dr. Spencer** *has received research/grant support, is a consultant for, and/or is a member of the speakers' bureaus of Abbott, Boston Life Sciences, Bristol-Myers Squibb, Cephalon, Celltech, Eisai, Eli Lilly, GlaxoSmithKline, Novartis, Ortho-McNeil, Pfizer, Shire Richwood, and Wyeth;* **Dr. Wozniak** *has received research/grant support from and is a major stock shareholder of Eli Lilly and has received honoraria from and is a member of the speakers'/advisory boards of Eli Lilly and Janssen.*

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Overview of ADHD

Joseph Biederman, M.D., opened the symposium by reviewing the history of attention-deficit/hyperactivity disorder (ADHD), neurologic impairment in individuals with ADHD, and the prevalence of the disorder and comorbid conditions. Dr. Biederman also explained how, together, symptoms and comorbid conditions result in the impairments associated with ADHD.

History of ADHD

Dr. Biederman noted that in 1902, George Frederic Still, M.D., made an invaluable contribution to the conceptualization of ADHD. Dr. Still[1] proposed that defiance, excessive emotion, and impaired inhibition in children were most likely caused by a genetic dysfunction and not by poor child rearing as many people had previously believed. In 1937, pediatrician Charles Bradley[2] advanced the treatment of ADHD-like symptoms when he discovered that a formulation of the stimulant amphetamine (Benzedrine) reduced symptoms of hyperactivity, inattention, and impulsivity in children.

Between the 1940s and 1980s, this collection of behavioral symptoms was treated under several names such as *minimal brain dysfunction* and *hyperkinetic syndrome*. In 1980, the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III)[3] included the diagnosis of attention deficit disorder, with the first definition of an ADHD-like disorder in adults. The criteria and name for this disorder were updated in 1987 in the DSM-III-R[4] and finally evolved to its most recent identity, attention-deficit/hyperactivity disorder, in the DSM-IV[5] in 1994.

Characteristics of ADHD

According to the DSM-IV criteria,[5] the impairment associated with ADHD must have been present for at least 6 months before the diagnosis can be made. The types of ADHD, from least to most common, are predominantly hyperactive, predominantly inattentive, and combined. The disorder begins before an individual is 7 years old, and the average age at onset is 3 or 4 years. Individuals with ADHD face deficits in 2 or more settings such as school, work, and home. An individual's symptoms generally evolve as he or she ages. For example, hyperactivity might subside into restlessness by adulthood. Also, the potential impairment of ADHD increases as individuals gain responsibility and are involved in more relationships and activities.

Prevalence of ADHD

Dr. Biederman related that depending on the region and criteria used to define ADHD, an estimated 3% to 9% of children worldwide have the disorder.[6] Perhaps 30% to 85% of children with ADHD continue to have the disorder in late adolescence and young adulthood.[7–10] In addition, ADHD appears highly heritable. First-degree relatives of a child with ADHD are at 4.6-fold to 7.6-fold increased risk for developing the disorder compared with relatives of normal controls or controls with psychiatric disorders other than ADHD.[11] The highest incidence of

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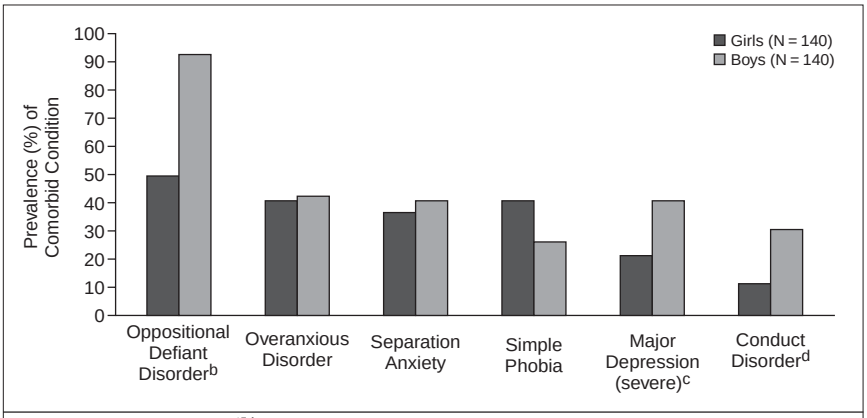
Table 1. Prevalence of ADHD or ADHD Symptoms in Parents of Children With ADHD and Controls[a]

Study	Prevalence in Mother		Prevalence in Father	
	Child With ADHD, %	Child Without ADHD, %	Child With ADHD, %	Child Without ADHD, %
Cantwell, 1972[7]	4	0	16	2
Reeves et al, 1987[12]	3	0	0	0
Biederman et al, 1990[11]	19	0	44	8

[a]Diagnostic criteria: hyperactivity in Cantwell; *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III) attention deficit disorder in Reeves et al. and Biederman et al.

Figure 1. Prevalence of Comorbid Conditions in Boys and Girls With ADHD[a]



[a]Data from Biederman et al.[17] [b]$p < .001$ for between-group difference. [c]$p = .001$ for between-group difference. [d]$p = .002$ for between-group difference.

ADHD might be in parents of children with the disorder (Table 1).

Brain Findings in Individuals With ADHD and Controls

Dr. Biederman reported that a neurologic basis might underlie the disorder. In a study of 152 children and adolescents with ADHD and 139 controls, Castellanos et al.[13] found that individuals with ADHD had substantially smaller cerebellar, temporal gray, and total cerebral volumes than controls. Unmedicated patients with ADHD had significantly ($p < .001$) smaller white matter volumes than controls and medicated individuals with ADHD. Smaller brain volumes were also correlated with worse scores on the Clinical Global Impressions-Severity of Illness scale and age-appropriate Wechsler Intelligence Scales, regardless of the individual's medication status.

Zametkin et al.[14] examined the possible relationship between brain glucose metabolism and ADHD. Positron emission tomography (PET) scans were performed in 55 adult controls and 25 adults who had ADHD, had not received stimulant treatment, and were the parents of children with ADHD. The PET scans revealed that global cerebral glucose metabolism and normalized regional glucose metabolism in parts of the frontal lobe, primarily the premotor and somatosensory cortex, of the brain were significantly ($p \leq .05$) lower in patients than controls.

Dr. Biederman also stated that the norepinephrine and dopamine neurotransmitter systems affect the attentional systems in the brains of individuals with ADHD. In the posterior attentional system, the noradrenergic system works to disengage one's focus from stimuli and engage attention to new stimuli.[15] Both the noradrenergic and dopaminergic systems in the anterior attentional system help an individual to analyze data and prepare to respond.[15] Modulation of noradrenergic and dopaminergic systems may be the action through which medications improve symptoms of ADHD.

Comorbid Conditions and ADHD

Dr. Biederman mentioned that most individuals with ADHD have a comorbid condition. At least 1 comorbid condition was present in 87% of the 15 children with DSM-III-R ADHD and 71% of the 42 children with subthreshold ADHD in a study[16] of 409 Swedish children. The prevalence of 2 or more comorbid conditions was 67% in the children with full ADHD and 36% in those with subthreshold ADHD. Oppositional defiant disorder is the condition most commonly comorbid with ADHD in both girls and boys (Figure 1).

Formula for Impairments Associated With ADHD

Dr. Biederman explained that, together with comorbid conditions, the symptoms of ADHD cause the functional impairments seen throughout the lives of individuals with the disorder. Impairments at school or work include academic difficulties, underachievement, and difficulty with authority. At home, individuals with ADHD might be unwilling to do chores and/or homework, defy parents' instructions, and engage in disruptive or destructive play. Social impairments such as poor peer relationships, aggression, and difficulty relating to others might also result from the symptoms of ADHD and comorbid conditions.

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Appropriate Therapeutic Targets for ADHD

Janet Wozniak, M.D., defined the concepts used in establishing therapeutic targets and then listed impairments related to ADHD that are commonly associated with different stages of development. She also explained how a single symptom can cause impairments throughout the day in multiple settings. Finally, Dr. Wozniak gave advice on setting and monitoring therapeutic targets in ADHD.

Terminology Used in Establishing Therapeutic Targets

Dr. Wozniak explained the differences in symptoms, impairments, and functional outcomes in the context of ADHD (Table 2). The core symptoms of ADHD—inattention, hyperactivity, and impulsivity—may be common in many individuals with and without the disorder. Therefore, evaluating the degree of impairment caused by the symptoms of ADHD may be more helpful in making a diagnosis than merely identifying the symptoms. These specific impairments and the resulting functional outcomes can then be targeted with treatment.

Table 2. Difference in Symptoms, Impairments, and Functional Outcomes

Term	Definition	Example
Symptoms	Overt manifestations of the disorder	Hyperactivity, impulsivity, inattention
Impairments	Adverse effects that result from core symptoms and differ with the patient's stage of development	Impaired academic performance
Functional outcomes	Results of symptom-related impairments	Impaired self-esteem

Potential Impairment Associated With ADHD by Age Category

Impairments associated with ADHD in all age groups can cause problems for not only individuals with the disorder but also the people with whom they interact. Dr. Wozniak listed some impairments that are most common or begin during certain ages.

Preadolescence. Impairments in school-age children with ADHD can cause problems in their relationships with their families, teachers, and peers.[1,2] At home, these children might disrupt family routines and cause their parents a tremendous amount of stress. At school, children with ADHD might have academic difficulties associated with their distractibility. Also, behaviors such as blurting out answers might alienate children from their teachers.

Problems with peers might stem from playing games uncooperatively, giving instructions that seem bossy, and becoming easily frustrated. Uncooperative behavior might also lessen children's participation in team sports because coaches might think these children have attitude problems. Social impairment can also include impulsively making inappropriate comments, lying, and performing more disturbing behaviors such as stealing, destroying property, and being cruel to other people and animals.

Because many children with ADHD procrastinate and have poor planning skills, they often have difficulty with hygiene issues such as establishing regular, healthful patterns of sleeping and eating.

Adolescence. Adolescents with ADHD often have impairments with greater potential consequences than do school-age children with ADHD. The easy frustration in childhood might develop into anger and mood lability in adolescence. Adolescents with ADHD are at greater risk than are those without ADHD for alcohol and substance abuse and addiction as well as smoking.[1] Difficulty with authority and criminal behavior might also be more common in adolescents with ADHD.[1]

The impulsivity and poor planning associated with ADHD might also lead to higher rates of sexually transmitted disease and teenage pregnancy among affected individuals than among those without ADHD.[2] Motor vehicle accidents and violations, which can affect the public, are also more common among adolescents with ADHD than among their peers.[3]

Another important impairment that the symptoms of ADHD can cause in adolescents is low self-esteem. For example, adolescents with ADHD might be disappointed by having to work harder to make good grades than their intelligence-matched peers do.

Adulthood. ADHD is being increasingly recognized as a diagnosis that persists after childhood. However, clinicians may have difficulty diagnosing

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Table 3. Impairments Caused by Multiple ADHD Symptoms in a Child

	Area of Impairment			
Symptom	Home	School	Social	Self
Hyperactivity	Interferes with dinner and bedtime routines	Runs around the classroom	Disrupts games	Feels rejected
Impulsivity	Interrupts conversations	Disrupts class	Is excluded from social events	Gets into trouble often
Inattention	Has difficulty finishing homework	Gets behind in schoolwork	Cheats in games	Thinks of self as unintelligent

adults with ADHD because associated impairments such as substance abuse, depression, and suicidal behavior might obscure the core symptoms of ADHD.

Impairments in regulating motivation and choosing the best response to a situation might lead to occupational difficulties.[2] Even individuals with ADHD who are doing well in their careers might be working harder or be more reliant on the support of staff or family to achieve the same amount of success as their peers. Problems with organization, meeting deadlines, and procrastination can often cause individuals with ADHD to be fired.

Another area of impairment in adults with ADHD is marital and social distress.[1] ADHD symptoms and functional impairments can lead to the need for marital counseling, separations, divorce, and multiple marriages.

Multiple Impairments Caused by Single Symptoms

Dr. Wozniak stated that any of the 3 core symptoms of ADHD can cause impairment in any aspect of life. For example, a single symptom of ADHD might affect a child's behavior in more than one setting (Table 3). Continuous symptom relief would help control the impairment that individuals with ADHD face throughout the day.

Setting and Monitoring Therapeutic Targets

The first step Dr. Wozniak gave for setting therapeutic targets was interviewing the patient and family regarding core symptoms of ADHD. Physicians should also evaluate the presence of risk and protective factors that can alter the course of ADHD. These factors include the presence of comorbid conditions and the level of intellectual functioning. Determining the specific impairments and which symptoms cause them in the individual is also useful for setting therapeutic targets.

Dr. Wozniak noted that once targets have been established, an individualized treatment program can begin. After treatment has begun, the physician should monitor side effects and evaluate the effect of treatment on the core symptoms and specific impairments. Once the degree of therapeutic improvement and side effects have been assessed, the physician should adjust or maintain treatment to reduce the major impairments and achieve the desired functional outcomes throughout the day.

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Standard Approaches to Treating ADHD

Christopher J. Kratochvil, M.D., spoke about current standard ADHD treatments, i.e., behavioral modification and stimulants. Few data exist on the use of behavioral modification in adults; therefore, Dr. Kratochvil focused on children and adolescents. Also, most information on stimulant treatment in ADHD is about children and adolescents, not adults.

Behavioral Modification

An important point about behavioral modification is that such interventions should be provided consistently across all areas in which the patient has difficulty, according to the American Academy of Pediatrics guidelines.[1] For example, behavioral modifications should focus on not only academic functioning but also social functioning, including the patient's relationships with peers. Also, training both parents and teachers in providing behavioral therapy will help present the child with consistent expectations and methods for improving his or her behavior at home, at school, and in social settings.

The short-term effectiveness of behavioral therapy is well documented, but because little evidence shows that the gains made during behavioral therapy will persist once treatment is stopped, Dr. Kratochvil stressed that families, clinicians, and teachers need to be aware that long-term maintenance treatment is necessary to achieve long-term behavioral gains.

Recommended techniques of behavioral therapy. Dr. Kratochvil listed several research-supported techniques from the American Academy of Pediatrics guidelines.[1] One technique is positive reinforcement, which is providing rewards or privileges to the child who performs desired behaviors. Similarly, the response-cost system entails withdrawing rewards or privileges from children when they act out.

Another effective technique is putting the child in time-out, i.e., sending the child to a quiet place to calm down, when he or she disobeys or behaves inappropriately. Dr. Kratochvil stated that he and other experts recommend placing the child in time-out for approximately 1 minute per year of age; that is, a child who is 6 years old would be put in time-out for 6 minutes.

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The token economy technique combines the positive reinforcement and response-cost systems. With the token economy, a child can see tangible benefits of behaving and disadvantages of misbehaving. For example, a parent or teacher could keep track of a child's behavior with stickers or coins. When the child does something desirable, he or she will receive a sticker on a chart or a coin. If the child misbehaves, the parent or teacher will take away a sticker or coin. At the end of an established period of time, e.g., a week, the child would be allowed to turn in the stickers or coins he or she has accumulated for a reward. Small rewards such as candy would cost the child fewer stickers or coins than more desirable rewards such as having a friend sleep over or going to the movies.

Recommended environmental modifications. Some environmental modifications might reinforce parents' and teachers' efforts to improve children's behavior. Dr. Kratochvil said that although these environmental changes are not robustly supported by the literature, clinical evidence shows that these adjustments might have an important impact on the behavior of children and adolescents with ADHD. One recommended modification is providing the child with a more structured environment. For example, parents and teachers could set schedules for children to follow throughout the day.

Another helpful environmental change is moving the child to a spot in the classroom where closer supervision by and interaction with the teacher is possible.

Dr. Kratochvil also suggested limiting distractions. At school, children with ADHD could sit away from other students or in a cubicle when they need to focus on a task. When trying to concentrate on an activity such as reading or doing homework at home, they should go to a part of the house where they will be least distracted by toys, television, and other individuals.

Training parents to implement behavioral therapy. Parents who provide behavioral therapy can improve children's behavior and their relationships with their parents, siblings, and other family members. Dr. Kratochvil reviewed the guidelines of the American Academy of Pediatrics[1] for training parents to implement behavioral therapy.

Initially, parents and the child should frequently meet with the therapist who is providing the behavioral therapy training so that the parent can learn how to use the behavioral methods and the child can learn what to expect. As parents become comfortable with the techniques, contact with the therapist can become less frequent. Parents must remember that for parent-implemented behavioral therapy to be effective, they must consistently carry out their techniques not only in the therapist's office but more importantly at home.

For as long as necessary, possibly years, the therapist should periodically contact the parent to inquire about the child's progress and provide support. The therapist should also help the parents establish a plan for maintaining improvements in the child's behavior and preventing relapse with continued use of behavioral techniques, especially during times when the child is experiencing stress. Once contact between the therapist and parents has become infrequent, the therapist and parents should continue to communicate when the child is undergoing major developmental transitions such as entering adolescence.

Training teachers to implement behavioral therapy. Dr. Kratochvil emphasized that teacher-implemented behavioral therapy will be successful only if the teacher can see its value and is prepared to participate. The focus of teacher-implemented therapy is the child's classroom behavior, academic performance, and peer relationships.

When training begins, the behavioral therapist should work with the teacher often. Once the teacher is able to implement behavioral therapy without frequent input from the therapist, the therapist should remain available for the teacher to call in case difficulties with the student's behavior arise.

Like parents, teachers need to have a plan for maintaining desired behaviors and preventing the return of misbehavior. Because children generally have different teachers and must adjust to a new environment each year, maintenance programs at school are particularly important. If all school staff, including administrators, were trained to implement behavioral therapy, the child's transition to a new classroom would go more smoothly. The therapist can establish the maintenance program, but eventually parents could be trained to direct the program. Teachers should be able to reach the therapist during major developmental transitions in the child's life such as the progression from childhood to adolescence when the child moves from grade school to junior high.

Stimulant Treatment

Stimulants are effective in reducing the ADHD core symptoms, i.e., inattention, impulsivity, hyperactivity, in 65% to 75% of individuals with the disorder.[2] Other impairments or problems associated with ADHD might be improved with stimulant therapy as well: poor compliance with treatment, impulsive aggression, and academic performance.[2] However, meta-analyses

Table 4. Effect Size of Stimulants on Behavior and Attention and IQ and Academic Achievement in Meta-Analyses of Treatment of Individuals With ADHD[a]

	Area of Improvement	
Study	Behavior and Attention	IQ and Academic Achievement
Kavale, 1982[3]	.804	.491
Ottenbacher and Cooper, 1983[4]	.96	.47
Thurber and Walker, 1983[5]	.746	.229

[a]Behavior and attention were defined as behavior outcomes in Kavale,[3] behavioral/social in Ottenbacher and Cooper,[4] and attention and distractibility in Thurber and Walker.[5] IQ and achievement were defined as cognitive outcomes in Kavale, IQ achievement in Ottenbacher and Cooper, and school achievement in Thurber and Walker.

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from the early 1980s[3–5] show that stimulants generally have a greater effect on the core symptoms such as attention than on impairments such as in IQ and academic achievement (Table 4).

Dr. Kratochvil also reported that the literature and clinical experience show that different stimulants are generally of equal efficacy in ADHD.

Prescribing stimulants. The stimulants most commonly used in ADHD are amphetamines and methylphenidate. Like the formulations themselves, the dosing guidelines for these drugs are similar. Drug doses should be gradually increased until the therapeutic level, i.e., the dose that improves the patient's symptoms and causes only minimal side effects, is reached.

Often, with immediate-release formulations of amphetamines and methylphenidate, individuals with ADHD take a dose of medication when they wake in the morning and then 1 or 2 additional doses at intervals of 4 to 6 hours throughout the day. According to the *Physicians' Desk Reference*, the maximum daily dose should not exceed 40 mg for amphetamines[6,7] and 60 mg for immediate-release formulations of methylphenidate,[8] especially for children 6 to 12 years of age. Dr. Kratochvil noted that sometimes higher doses are needed to achieve response; finding the appropriate dose and medication should be guided by the individual's response.

Measuring the effects of stimulants. Dr. Kratochvil noted the importance of monitoring medication effectiveness during titration and periodically throughout treatment. One technique is having parents or teachers record improvement in target outcomes for the child on a behavior report card. A behavioral rating scale such as one based on the symptoms of ADHD listed in the DSM-IV[9] could help physicians evaluate the change in core symptoms with different medication doses. For children and adolescents, parents or teachers might be the most reliable source of information on the patient's behavior. Adults might be able to complete their own behavioral rating scales. For each patient, how long each dose of medication is effective should also be reported.

In addition to monitoring the improvement in ADHD symptoms, physicians should evaluate the side effects of stimulant therapy. Parents or teachers of children and adolescents with ADHD and adult patients might complete a side effect checklist and report any new or severe adverse events to their physicians.

Table 5. Efficacy in Clinical Trials of New Stimulant Formulations in Children and Adolescents With ADHD[a]

Study	Drug	Trial Design	Length of Treatment	Intent-to-Treat Population	Findings
Biederman et al[10]	Adderall XR (amphetamine and dextroamphetamine)	Multicenter, double-blind, randomized, placebo-controlled, parallel-group	3 wk	563	Differences between baseline and endpoint scores on the teacher-completed Conners' Global Index were significantly ($p < .001$) greater for each of 3 doses (10, 20, and 30 mg/d) of active medication than for placebo
Greenhill et al[11]	Metadate CD (methylphenidate)	Multicenter, double-blind, randomized, placebo-controlled	3 wk	314	Weekly, morning, and afternoon scores on the teacher-completed Conners' Global Index were significantly ($p < .0001$) lower with active medication than with placebo
Biederman et al[12]	Ritalin LA (methylphenidate)	Multicenter, double-blind, randomized, placebo-controlled	2 wk	134	Changes in baseline and endpoint scores on the Conners ADHD/DSM-IV Subscales for Teachers were significantly ($p < .0001$) greater with active medication than with placebo
Wolraich et al[13]	Concerta (methylphenidate)	Multicenter, double-blind, randomized, placebo-controlled, parallel-group	4 wk	282	Endpoint scores on the IOWA Conners Inattention/Overactivity subscale were significantly ($p < .05$) lower with immediate-release methylphenidate or Concerta than with placebo
Conners et al[14]	Focalin (dexmethylphenidate)	Randomized, double-blind	4 wk	132	Medication or placebo was given daily at 8 am and noon; at 3 pm, scores on the parent-rated SNAP-IV were significantly ($p \leq .004$) lower with *d*-methylphenidate and *d,l*-methylphenidate than with placebo; at 6 pm, scores were significantly lower for only *d*-methylphenidate than for placebo

[a]The appropriate stimulant dose for each patient was determined based on response to previous treatment or during an immediate-release titration period in all trials.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, SNAP-IV = Swanson, Nolan, and Pelham, version IV, parent and teacher rating scale.

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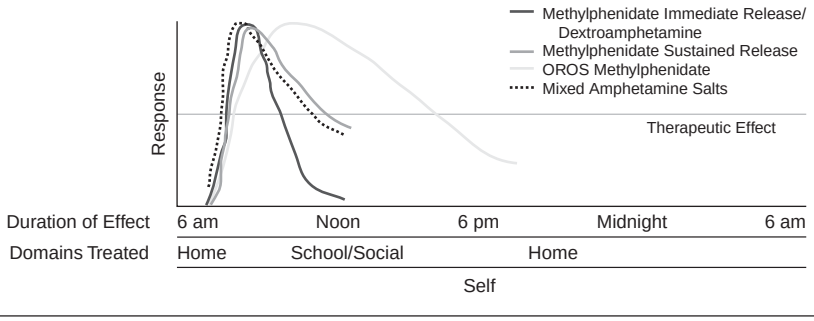
Figure 2. The Duration of Effect of a Single Dose of a Stimulant Formulation on Symptoms of ADHD[a]



[a]With permission from the National Alliance for the Advancement of ADHD Care (NAAAC) and data from Wilens and Spencer.[2]

New stimulant formulations. Recently, several new extended-release formulations of stimulants have become available. Dr. Kratochvil described how several of the new delivery options work and cited studies[10–14] demonstrating the effectiveness of these medications (Table 5).

Three stimulant preparations that use immediate-release and delayed-release beads of medication were approved by the U.S. Food and Drug Administration (FDA) in 2001 and 2002. Adderall XR is a mixture of 75% dextroamphetamine and 25% levoamphetamine salts.[15] Both Metadate CD and Ritalin LA are extended-release capsules of methylphenidate.

When a patient takes Adderall XR, the medication in half of the beads is released immediately, and the medication in the other half is released about 4 hours later.[16] With Metadate CD capsules, 30% of the beads are released immediately and 70% about 3 hours later.[17] Capsules of Ritalin LA contain 50% immediate-release and 50% delayed-release beads and result in 2 peak plasma drug concentrations that occur about 4 hours apart.[18]

Patients who find swallowing pills difficult may take any of these 3 delayed-release stimulant formulations by opening the capsule, sprinkling the beads in applesauce, and immediately swallowing the mixture without chewing.[15,17,18]

Another extended-release formulation of methylphenidate, Concerta, uses a different technology than the combination of immediate-release and delayed-release beads. With the osmotic, controlled-release OROS delivery system, the plastic capsule is not digested.[19] Instead, methylphenidate is pushed out of the capsule's semipermeable membrane as water is pulled in. Also, the capsule is coated with short-acting methylphenidate. Therefore, individuals who take Concerta receive the equivalent of about 3 doses of immediate-release methylphenidate for approximately 12 hours of symptom relief.

A new immediate-release oral formulation of methylphenidate was also developed in recent years. Researchers isolated the *d*-isomer of methylphenidate from the *l*-isomer to result in dexmethylphenidate (Focalin). Because this medication has only the *d*-isomer, dexmethylphenidate can be prescribed at doses about half those of methylphenidate.[20] In addition, dexmethylphenidate appears to have a longer duration of action than methylphenidate.[14]

One new stimulant formulation that is still under investigation is the methylphenidate transdermal patch. Dr. Kratochvil said that possible benefits of this delivery system include the drug bypassing metabolism in the liver and physicians choosing the dose by administering the appropriate-sized patch. Also, the duration of action of the drug could be controlled by leaving the patch on the skin for only as long as medication delivery is desired.

Duration of effect of stimulant treatment in ADHD. Dr. Kratochvil cited a review by Wilens and Spencer[2] that compared the duration of action of a few agents (Figure 2). Although the long-acting stimulant formulations had a longer therapeutic effect than did immediate-release formulations, no single dose of a stimulant relieved ADHD symptoms for more than 12 hours per day.

Therefore, Dr. Kratochvil pointed out that multiple daily doses of a stimulant may need to be prescribed for a patient to experience continuous symptom relief.

Effectiveness of Behavioral Modification, Stimulant Treatment, and the Combination

Dr. Kratochvil addressed the relative efficacy of different standard strategies for treating ADHD. The Multimodal Treatment Study of Children With ADHD (MTA)[21] evaluated the treatment of 579 children. Each child received 1 of 4 treatments: medication management with an algorithm alone; behavioral therapy alone; multimodal treatment with medication management and behavioral therapy; or community care, e.g., stimulant treatment without an algorithm.

Although all 4 treatments substantially reduced the core symptoms of ADHD, medication management alone and multimodal treatment were significantly ($p < .001$) superior to community care. Medication management alone and multimodal treatment were also significantly ($p \leq .005$) more effective than behavioral therapy alone in reducing parent and teacher ratings of inattention and parent ratings of hyperactivity/impulsivity. Differences between medication management alone and multimodal treatment were not significant.

Secondary analyses by Swanson et al.[22] focused on the clinical importance of the MTA study. Swanson et al. defined excellent response to treatment as an endpoint score ≤ 1.0 on the Swanson, Nolan, and Pelham, version IV, parent and teacher rating scale. With this criterion, 68% of the children who received combination therapy, 56% of those on medication management, 34% of those who had

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behavioral therapy, and 25% of those who experienced community care were excellent responders at the 14-month endpoint. Therefore, the MTA demonstrated that adding behavioral therapy to medication treatment might be beneficial even though the improvement in ADHD symptoms was not significantly greater for combination therapy than for medication management alone in the primary findings.

Need for New ADHD Treatments

Dr. Kratochvil concluded by explaining that although stimulant and behavioral treatments, the current standard approaches to treating ADHD, are effective, these treatment options have some limitations. For example, ADHD treatments should work from the time the patient gets up in the morning until he or she goes to bed at night. Although the OROS formulation of methylphenidate is effective for up to 12 hours, no stimulant preparation will work for an entire 24-hour period unless multiple doses are prescribed. Also, because ADHD is a chronic disorder, treatment should focus on long-term improvement. With behavioral therapy, benefits last only as long as treatment is administered.

The MTA showed that medication management, alone or in combination with behavioral therapy, is key to effectively reducing ADHD symptoms. Stimulant treatment robustly improves core ADHD symptoms in 65% to 75% of patients.[2] However, certain individuals may not respond to stimulants or may be unable to tolerate potential adverse events such as decreased appetite, sleep disturbances, mood lability, and exacerbation of comorbid tic disorders. Unfortunately, stimulants are also schedule II drugs with a potential for abuse that might make some patients or their parents reluctant to accept these medications, despite the possible benefits. Therefore, nonstimulant medications might provide additional benefits for some individuals with ADHD.

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Nonstimulant Medication Treatments for ADHD

Thomas J. Spencer, M.D., presented information on nonstimulant medications and their potential for relieving symptoms of ADHD in multiple domains throughout the day.

Dr. Spencer noted that nonstimulant medications might have some advantages. For example, a medication that could be given in a single daily dose and reduce symptoms and related impairments throughout the entire day would be optimal. Symptoms of comorbid conditions such as tics, anxiety, or mood disorders in individuals with ADHD might not be exacerbated or improve with nonstimulant medications.

The medications that reduce symptoms of ADHD often work on the norepinephrine and/or dopamine neurotransmitter systems in the brain. Several nonstimulant medications have been studied and used off-label for ADHD. Dr. Spencer addressed the advantages and disadvantages of some of the most commonly used or most promising nonstimulant treatments in ADHD: antidepressants such as tricyclic antidepressants (TCAs), bupropion, and venlafaxine as well as

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atomoxetine, the only nonstimulant treatment approved by the FDA for ADHD.

Tricyclic Antidepressants

Dr. Spencer remarked that open and controlled trials of TCAs such as desipramine[1–5] and imipramine[6–9] have shown these agents to be efficacious in the off-label treatment of ADHD in children and adults. TCAs also have a longer duration of action than do stimulants, and a single dose might relieve ADHD symptoms throughout the entire day.[1,8]

TCAs have limitations because of their effects on systems other than the noradrenergic and dopaminergic systems. Anticholinergic effects can cause dry mouth and constipation. Antihistaminergic effects include sedation and weight gain, and α-adrenergic effects include blood pressure changes and tremor. TCAs are also associated with the potential for delayed cardiac conduction and repolarization, which might lead to sudden death.

Bupropion

Bupropion is another medication used primarily for depression that has also been studied in ADHD. Open[10,11] and controlled[12,13] trials have demonstrated bupropion's efficacy in children and adults with ADHD. Another benefit of bupropion is that it is not a controlled substance with a potential for abuse. However, because bupropion has been studied less in ADHD than have TCAs and stimulants, the effect size of bupropion is less well established. Bupropion's side effects include irritability, insomnia, and, rarely, seizures.

Venlafaxine

Dr. Spencer stated that venlafaxine is an antidepressant that has been proposed for treating ADHD off label. Advantages of venlafaxine are that open trials[14–17] have shown the drug to be efficacious in reducing the symptoms of ADHD in children and adults and that both immediate-release and sustained-release formulations of the drug are available for dosing flexibility. Unfortunately, no controlled trials have been conducted to solidly establish the effectiveness of venlafaxine in treating symptoms of ADHD. Side effects include irritability, insomnia, and gastrointestinal disturbance.

Atomoxetine

As indicated by recent FDA approval, atomoxetine is the only nonstimulant with extensive testing of safety and efficacy in ADHD. Dr. Spencer described how atomoxetine is believed to work in ADHD and cited several studies[18–21] that support the medication's use in the disorder.

Neurotransmitter effects. Dr. Spencer explained that atomoxetine is a specific norepinephrine reuptake inhibitor with a high affinity for the norepinephrine system and a low affinity for other neurotransmitter systems.[22] Therefore, atomoxetine appears unlikely to cause antihistaminergic or anticholinergic side effects. The drug is thought to enhance signal processing by inhibiting norepinephrine reuptake and, therefore, increasing norepinephrine levels.

Atomoxetine affects the dopaminergic system less than the noradrenergic. Dopamine levels are not increased in the nucleus accumbens or the striatum, areas believed to be related to abuse liability and tics, respectively. However, atomoxetine is associated with a downstream increase of dopamine levels in the prefrontal cortex, which is the part of the brain linked with working memory, ability to rehearse responses, and level of impulsivity.

Efficacy in ADHD. Atomoxetine trials have focused on a variety of outcomes: short-term efficacy versus placebo, efficacy versus stimulants, duration of effect, and long-term efficacy.

Short-term efficacy versus placebo. Dr. Spencer reported that the average effect size of atomoxetine was about 0.7 in 6 placebo-controlled, multicenter atomoxetine trials, which included more than 1000 children with ADHD (data on file, Eli Lilly and Company, Indianapolis, Ind.).

Dr. Spencer discussed the effects of atomoxetine in 2 identical, 12-week, randomized, double-blind, placebo-controlled trials[20] in 291 children with ADHD. In the first trial, the children taking atomoxetine had significantly ($p < .001$) greater changes between baseline and endpoint total ADHD Rating Scale and inattention and hyperactive/impulsive subscale scores than did children taking placebo (Figure 3). Similar reductions in total and subscale ADHD Rating Scale scores were also seen in the second trial. Therefore, improvement with atomoxetine occurs in both core symptom domains of ADHD.

Efficacy versus stimulants. No adequately powered studies have compared atomoxetine with a stimulant, the current standard medication treatment for ADHD. However, Dr. Spencer stated that the effect sizes from the atomoxetine trials and a meta-analysis[23] of methylphenidate trials indicate that the 2 drugs have similar efficacy in ADHD. 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. This effect size of methylphenidate is similar to that found in atomoxetine trials (about 0.7).

A randomized, 10-week, open study[19] of 228 children with ADHD also compared the effect sizes of atomoxetine and methylphenidate. Dr. Spencer noted that in this study, atomoxetine and methylphenidate had almost equal effects on total, inattentive, and hyperactive/impulsive symptoms of ADHD (Figure 4).

Duration of effect. According to the results of 2 unpublished studies Dr. Spencer described, a single dose of atomoxetine given in the morning is effective in reducing children's ADHD symptoms throughout the day. The first study (A. J. Allen, M.D., Ph.D.; R. Tannock, Ph.D.; M. Weiss, M.D., Ph.D.; et al., unpublished data, 2002) reported outcomes in the school setting. In this 7-week study, changes between baseline and endpoint in scores on the teacher-rated Conners Global Index and the Teacher Behavior Problem Scale were significantly ($p < .05$) lower for the 74 children taking atomoxetine once daily than for the 42 children taking placebo.

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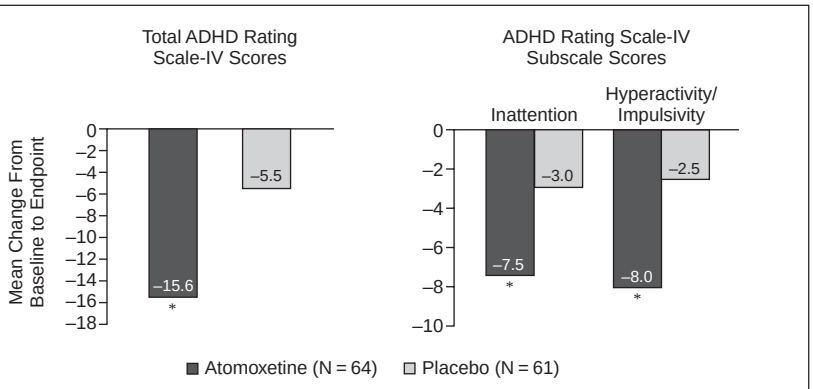
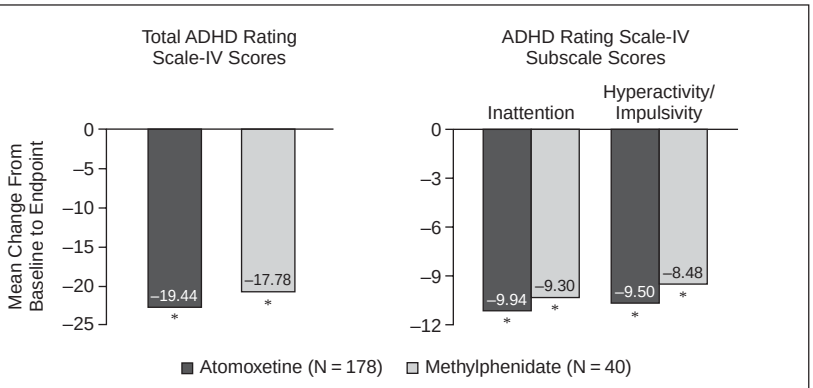
Figure 3. Change in ADHD Rating Scale-IV Scores Between Baseline and Endpoint for Children and Adolescents Treated With Atomoxetine or Placebo[a]



[a]Data from Spencer et al.[20] *p < .001 vs. placebo.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Figure 4. Change in ADHD Rating Scale-IV Scores Between Baseline and Endpoint With Open Atomoxetine or Methylphenidate Treatment in 218 Children (intent-to-treat population)[a]



[a]Data from Kratochvil et al.[19] *p < .001 for change within treatment group. Between-group differences were not significant.

The second study (D. Kelsey, M.D., Ph.D.; C. Sumner, M.D.; C. Casat, M.D.; et al., unpublished data, 2002) examined improvement in ADHD symptoms seen by parents of about 180 children over 7 days. After only 1 day of treatment, improvement in Daily Parent Rating Scale scores was significantly greater with atomoxetine than with placebo.

Kelsey and colleagues also found improvement in ADHD symptoms as measured by the Daily Parent Rating of Evening and Morning Behavior Scale. The change in behaviors on the Evening subscale such as completing homework, not arguing or struggling excessively, sitting through dinner, and transitioning from play or work to settling at bedtime was significantly greater with atomoxetine than with placebo. Functioning in the early morning, nearly 24 hours after the last medication dose, was also significantly more improved for children who took atomoxetine than those who took placebo. Improvements measured by the Early Morning subscale included getting out of bed and getting ready for school more quickly and easily and arguing and struggling less with parents and siblings.

Long-term efficacy. Dr. Spencer mentioned 2 studies that examined the efficacy of atomoxetine in ADHD for 8 or more months. Both trials had 3 phases: an acute-treatment phase, a brief discontinuation phase, and an extension phase with open-label atomoxetine treatment. In the 9-week acute treatment phase of the trial in children (T.J.S.; J. Heiligenstein, M.D.; J.B.; et al., unpublished data, 2002), atomoxetine was significantly ($p < .01$) more effective than placebo in decreasing mean ADHD Rating Scale scores. Although these scores increased during the discontinuation phase, scores were significantly ($p < .001$) reduced during the 76 weeks of open-label atomoxetine treatment.

Compiled results[21] from the 10-week acute phases of 2 identical trials showed that atomoxetine was associated with a significantly ($p \leq .008$) greater change in total Conners' Adult Attention Rating Scale scores between baseline and endpoint than was placebo. Patients also continued to experience improvement during the 34-week discontinuation phase (L. A. Adler, M.D.; D. Michelson, M.D.; T.J.S.; et al., unpublished data, 2002).

Improvement in functional outcomes. Although functional outcomes should be a target of ADHD treatment, Dr. Spencer said that few studies of medication effects on functional outcomes have been conducted. He cited a randomized, placebo-controlled, dose-response trial[18] of atomoxetine in children and adolescents that presented functional outcomes as secondary measures. Improvement seen with 0.5 mg/kg/day of atomoxetine was small. However, changes in several areas of individual and family functioning were significantly greater for the groups treated with 1.2 or 1.8 mg/kg/day of atomoxetine than for the group treated with placebo (Figure 5).

Safety. Dr. Spencer stated that the degree of physicians' confidence in a medication is related to the extent, i.e., in how many patients, the drug's safety and tolerability have been tested. He explained that testing a medication's safety in a large group of people will help identify any subgroup that might be especially vulnerable to adverse events.

At the time of Dr. Spencer's presentation, more than 4000 individuals had taken atomoxetine for any length of

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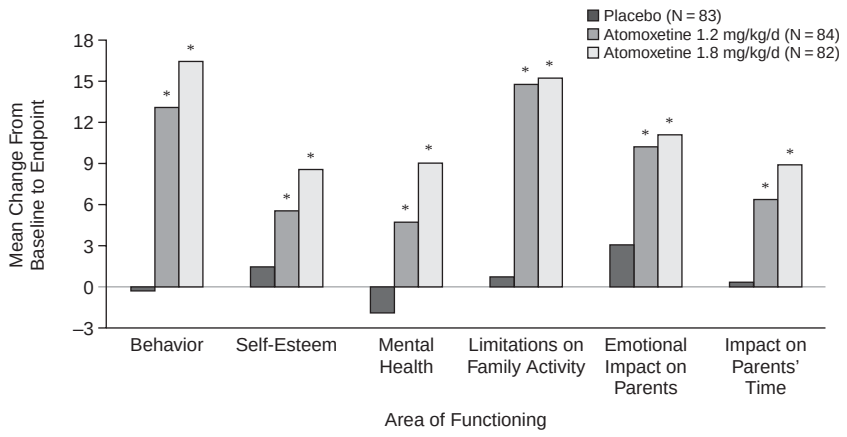
Figure 5. Improvement in Functional Outcomes as Measured by Mean Change in Child Health Questionnaire (CHQ) Scores for Children and Adolescents Taking 1.2 or 1.8 mg/kg/d of Atomoxetine or Placebo[a]



[a]Data from Michelson et al.[18] Higher scores on the CHQ indicate more favorable functioning. *p < .05 vs. placebo. A significant (p < .05) linear dose response was seen for all areas of functioning.

Table 6. Adverse Events Occurring in ≥ 10% of Any Treatment Group in the Combined Results of 2 Proof-of-Concept, Controlled Trials of Atomoxetine, Placebo, and Methylphenidate in Children and Adolescents[a]

Adverse Event	Atomoxetine (N = 129) %	Placebo (N = 124) %	Methylphenidate (N = 37) %
Abdominal pain	31.0	21.8	29.7
Headache	30.2	28.2	45.9[b]
Rhinitis	25.6	32.3	13.5[b]
Decreased appetite	21.7[b]	7.3	32.4[b]
Pharyngitis	16.3	15.3	10.8
Vomiting	14.7	12.1	13.5
Increased cough	13.2	11.3	16.2
Nervousness	13.2	6.5	16.2
Nausea	10.1	10.5	16.2
Somnolence	9.3	8.1	10.8
Insomnia	7.0	8.9	27.0[b,c]
Diarrhea	6.2	6.5	16.2
Fever	6.2	9.7	18.9[c]
Dizziness	3.9	4.0	13.5[c]

[a]Data from Spencer et al.[20] and Allen et al.[24] Data for the methylphenidate comparison were not reported in the published results by Spencer et al. [b]p < .05 vs. placebo. [c]p < .05 vs. atomoxetine.

time and more than 700 for over a year (data on file, Eli Lilly and Company, Indianapolis, Ind.).

Dr. Spencer referenced the combined results[20,24] of 2 trials in children and adolescents to indicate the tolerability of atomoxetine treatment (Table 6). Overall, atomoxetine was well tolerated. Dr. Spencer noted that atomoxetine's lack of association with insomnia was important because this medication's effects seem to last into the night. The only side effect that occurred in significantly (p < .05) more patients taking atomoxetine than those taking placebo was decreased appetite. Although the methylphenidate group was small, these safety data give an initial indication of atomoxetine's tolerability in comparison with methylphenidate.

Small changes in vital signs have also been noticed with atomoxetine treatment. Dr. Spencer reported that pulse increased by about 6 beats per minute and both systolic and diastolic blood pressure by about 1.5 mm Hg.[25] However, these changes were insignificant, and pulse and blood pressure normalized when treatment was discontinued. Atomoxetine did not have any other cardiac effects such as prolongation of the QTc interval.

During open-label studies of atomoxetine treatment lasting 12 months or longer, mean weight and height increased at rates consistent with age and gender norms (data on file, Eli Lilly and Company, Indianapolis, Ind.). Many patients might experience a small initial weight loss, but weight generally stabilized within 9 months of treatment.

Atomoxetine does not appear to exacerbate tics and anxiety, and investigators are currently conducting trials to determine whether the medication might actually improve these comorbid conditions.

Atomoxetine's place in the therapeutic armamentarium. Dr. Spencer concluded his presentation by explaining where atomoxetine's characteristics might place the drug in the armamentarium of treatments for ADHD. Like stimulants, atomoxetine improves ADHD's core symptoms and impairments in academic, occupational, social, and family functioning. However, atomoxetine has a longer duration of action. For some patients, a single dose of atomoxetine in the morning will provide continuous symptom relief throughout the entire day, evening, and next morning.

Changes in pulse and blood pressure appear to be comparable between atomoxetine and stimulant treatment. Like stimulants, atomoxetine is associated with decreased appetite. However, unlike stimulants, atomoxetine is not associated with insomnia and the potential for abuse. Therefore, clinicians, parents, and patients will not have to worry about the stigma or monitoring associated with controlled substances. The safety profile and/or efficacy of atomoxetine are also favorable compared with other nonstimulant treatments tried in ADHD such as TCAs, bupropion, and venlafaxine.

Dr. Spencer reminded the audience that, like other medications, atomoxetine is not effective for all patients with ADHD, although many individuals who have not responded to stimu-

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lant treatment might respond to atomoxetine. However, in choosing treatments, physicians should consider the individual patient's symptoms, impairments, and functioning.

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Drug names: *amphetamine and dextroamphetamine (Adderall and others), atomoxetine (Strattera), bupropion (Wellbutrin and others), desipramine (Norpramin and others), dexmethylphenidate (Focalin), dextroamphetamine (Dexedrine, Dextrostat, and others), imipramine (Tofranil and others), methylphenidate (Metadate, Ritalin, and others), venlafaxine (Effexor).*

Disclosure of off-label usage
To the best of his knowledge, Dr. Biederman has determined that bupropion, desipramine, imipramine, and venlafaxine have not been approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

To cite a section from this ACADEMIC HIGHLIGHTS, follow the format below:
Wozniak J. Appropriate therapeutic targets for ADHD, pp 267–268. In: Biederman J, chair. Determining and Achieving Therapeutic Targets in Attention-Deficit/Hyperactivity Disorder [ACADEMIC HIGHLIGHTS]. J Clin Psychiatry 2003;64:265–276

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