ADHD: TREATMENT AND OUTCOME*

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Chronic diseases and disorders are treated to reduce or eliminate symptoms and to minimize impairments. Like other chronic health problems, attention deficit hyperactivity disorder (ADHD) must be approached as a disorder that causes difficulties throughout the day, every day. Poor symptom coverage can cause poor outcomes. Thus, the treatment goal is to manage patients in such a way as to provide consistent daytime coverage of symptoms and associated behaviors.[1,2]

Clinicians are accustomed to asking their pediatric ADHD patients about school performance, but it is equally important to inquire about other aspects of functioning as well. How are they able to get along with their peers? How are things going with the family? These are areas that have not been addressed adequately when assessing and managing children with ADHD. The treatment goals for ADHD are not only to improve academic functioning but also to improve outcomes by improving functioning in nonacademic areas and the quality of relationships outside the classroom—relieving the frustration, anger, and poor self-image that typically impact more broadly on functioning and interpersonal relationships.[1] We know from the clinical evidence presented in Dr Gephart's review (page S160) that negative outcomes, such as substance abuse, smoking,[3] driving accidents,[1] and physical aggression,[4-8] increase dramatically in ADHD patients who are untreated.

Behavioral Interventions

When used concomitantly with pharmacotherapy, behavioral interventions have been proven effective in the treatment of children with ADHD. A long-term study sponsored by the National Institutes of Health looked at well-delivered pharmacotherapy, well-delivered behavioral therapy, combination therapy of the 2 approaches, and typical community care.[9] Those who received typical community care fared the worst, but these findings are revealing. They tell us that a systematic way of caring for children with ADHD is still lacking in the community and that when children are not treated systematically, they may not realize the greatest potential for benefit.

The study also demonstrated that for most ADHD symptoms, children in the combined treatment and the medication management groups showed greater improvement than those who were given intensive behavioral treatment without medication. However, children who received combined behavioral treatment with medication did not differ acutely in core ADHD outcomes compared with children treated with medication alone.[9]

The intensive behavioral modification strategies used within this study—delivered by highly trained behaviorists within the controlled and ideal framework of the clinical trial setting—are achieved elsewhere through systematic training of parents and teachers in behavioral therapy techniques. Strategies include environmental modifications, regulatory strategies, external aids, and psychosocial support. The goals of these behavioral interventions are to improve academic functioning and peer relationships. Behavioral interventions can particularly play a significant role in the management of children with anxiety or aggressive disorders that are comorbid with ADHD.[10] Additional evidence is being collected through ongoing Multimodal Treatment Study of Children with ADHD (MTA) evaluations to assess the long-term benefits of behavioral interventions to improve core ADHD symptoms.[2]

*Based on a presentation given by Dr Kratochvil at a symposium held in conjunction with the American Academy of Pediatrics 2003 National Conference and Exhibition.

ADHD Toolkit

To facilitate multimodal, multidisciplinary treatment, the American Academy of Pediatrics created a resource toolkit for clinicians, available at the National Initiative for Children's Healthcare Quality Web site: www.nichq.org/resources/toolkit/. This kit includes:

- Diagnostic checklists for teachers and parents
- Diagnostic tools for clinicians
- Treatment guidelines for selecting and implementing therapy plans, setting treatment goals, dosing medication, and managing side effects
- Parent information and support resources
- Information and sample forms for coding and billing

The important role of pharmacotherapy in the treatment of ADHD has been well documented in the medical literature and has been established conclusively by MTA findings.[9] Stimulants have been the cornerstone of ADHD therapy for decades. A variety of nonstimulant therapies have also demonstrated efficacy.

Stimulant Therapies with US Food and Drug Administration Indications

The 2 primary stimulants, amphetamine and methylphenidate (MPH), have been used since 1937 and 1957, respectively. Historically, one limitation of stimulant drugs was their short-acting profile. Over the past 10 years, however, long-acting stimulant formulations have changed the way that many clinicians have been able to manage ADHD. Extended release stimulants are advantageous because they are approved for first-line use in children and adolescents and have a 7- to 12-hour action profile, which varies with the formulation. However, they provide limited coverage in late evenings or early mornings, have the potential

for abuse and diversion, and have been linked with side effects such as decreased appetite and trouble falling asleep.[11,12]

Dextroamphetamine/ Levoamphetamine (Adderall XR®)

This long-acting stimulant contains 75% dextro and 25% levo-isomers of amphetamine salts. Its 10- to 12-hour action profile is achieved with a biphasic delivery system that releases 50% of the medication beads immediately and 50% approximately 4 hours later. For this reason, it is very important to instruct patients not to chew these capsules. Clinical investigations show that this compound is a viable therapeutic option and may be a clinical consideration, particularly for patients taking shorter-acting Adderall. The compound has been demonstrated to be effective for the treatment of ADHD, based on clinician and parent reports.[13]

MPH

Metadate® CD. This 20-mg formulation of MPH uses a biphasic bead delivery system that releases 30% of MPH (6 mg) immediately and 70% (14 mg) about 3 hours after dosing. The rationale for this formulation is based on the notion that tachyphylaxis occurs with steady blood levels of stimulant drugs. Increasing blood levels with a delayed drug burst is intended to provide sustained therapeutic benefit. This delayed-release medication has a duration of action of approximately 8 hours.[14]

Ritalin® LA. This drug uses a biphasic bead delivery system that releases 50% of the MPH as immediate-release beads and 50% as extended-release beads 4 hours later. Studies of this formulation show drug efficacy and a similar side-effect profile to that of MPH.[15]

Concerta®. This extended-release formulation of MPH is designed for a 10- to 12-hour effect, using an advanced extended-release delivery system. This capsule has a short-acting drug coating. It also features a laser-drilled hole at one end, creating an osmotic gradient that pulls water in and systematically pushes MPH out at timed intervals.[16]

Optimizing Response to Stimulants

Extended-release stimulants provide a longer duration of action than short-acting MPH, but immediate-release medications can still play a role in therapy. Dexmethylphenidate (Focalin™), for example, utilizes just 1 isomer of MPH for a 3- to 4-hour duration of action. This agent may be used in conjunction with a longer-acting drug, dosed several times per day, or perhaps used in some other situation in which it is necessary to sculpt the dose according to the individual patient.

Several factors come into play in optimizing the response to stimulants. First and foremost, the dose must be high enough to ensure full efficacy. Second, duration of action is an important consideration. How much time elapses before the drug becomes effective, and when do the effects wear off? As discussed by Dr Gephart, ADHD lasts all day, and management should extend beyond the school hours.

Sculpting the dose of the stimulants can be accomplished in several ways (Figure 1).[11] For example, if a patients needs 16 hours of coverage throughout the day, 2 doses of Metadate will last about 16 hours. Whereas the 10- to 12-hour coverage of other sustained-release stimulants may be adequate for some children, some may require the addition of a short-acting stimulant, such as Focalin or MPH, at the end of the day, when homework is being done.

Nonstimulant Therapy

Atomoxetine selectively blocks the reuptake of norepinephrine. As such, its pharmacokinetic profile differs from that of stimulants, and atomoxetine is not a Schedule II class drug. Whereas the stimulants take effect immediately, the onset of action of atomoxetine is more gradual, with full therapeutic effect sometimes occurring 4 to 5 weeks after initiating therapy. Its mechanism of action makes it an unlikely candidate for abuse.[17] Duration of efficacy is an even stronger advantage, as atomoxetine has demonstrated symptom control throughout the waking day (Figure 2).[18] Still, the medication is

Figure 1. Optimizing Response to Stimulants

IR = 4 hours	**Ritalin LA = 8 hours**
Metadate CD = 6-8 hours	**Concerta/Adderall XR = 10-12 hours**

- In general, use extended-release formulations
- Give first dose as early as possible in morning
- Increase dose to ensure maximum benefit
- Sculpt the dose
  - Give IR 3 times daily
  - Give Metadate CD or Ritalin LA twice daily
  - Give IR early morning and Concerta/Adderall XR around noon
  - Give Concerta/Adderall XR early and IR around 6 PM

IR = immediate release.
Data from Greenhill et al.[11]

not a panacea; reported side effects include gastrointestinal upset and tiredness.

Atomoxetine appears to have benefits into the evening and next morning, with positive impact on evening activities, including completing homework, settling at bedtime, and arguing.[19] Morning symptoms were also significantly improved with atomoxetine compared with MPH taken 3 times daily.[20] These initial findings of benefit in the morning and evening warrant further investigation, as does the efficacy of atomoxetine compared with stimulant therapy.

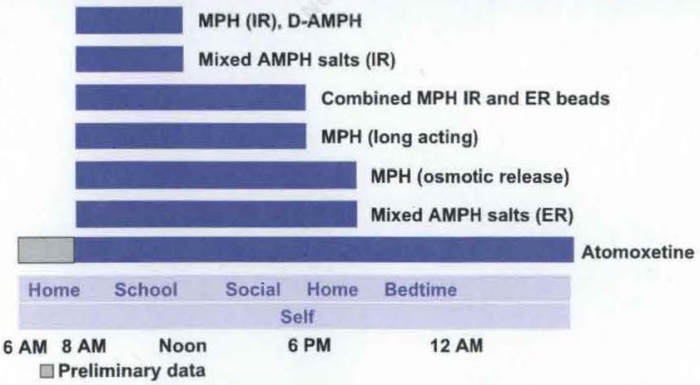
Optimizing Response to Atomoxetine

Although once-daily dosing is recommended for atomoxetine, early clinical trials were of twice-daily dosing. Therefore, if patients taking atomoxetine once daily experience tolerability problems, atomoxetine may be taken twice daily. The recommended starting dose is 0.5 mg/kg, given with food, then increased to 1.2 mg/kg for 2 weeks. The maximum approved dose is 1.4 mg/kg. A therapeutic trial of drug efficacy should be undertaken for at least 4 weeks. Consider cross-tapering if the patient is taking a stimulant. Some clinicians have found it useful to use a cross-titration (ie, cutting the dose of the stimulant in half) for a couple of weeks while ascending dose titration of atomoxetine. Somnolence associated with atomoxetine can be managed by dosing the medication following the evening meal.

Second- and Third-Line Options

Several antidepressants have been utilized in the treatment of ADHD, although none of them are approved by the US Food and Drug Administration for this indication. The tricyclic antidepressants are sometimes used in treatment of ADHD but would not be used as a first-line agent due to the side-effect profile, which includes concerns regarding cardiac side effects.[21] Bupropion has been shown to provide benefit for youths as well as adults with ADHD, but the evidence is weak and well-controlled trials of this medication have not been published. Bupropion does have the possibility of inducing seizures in susceptible patients.[22] It appears that monoamine oxidase inhibitors can reduce symptoms of ADHD as well,[23,24] but these drugs are rarely used for this indication because dietary restrictions are significant and the risk exists for cardiac crisis.

Figure 2. Stimulants vs Atomoxetine: Duration of Effect on ADHD Symptoms



MPH = methylphenidate; IR = immediate release; D-AMPH = dextroamphetamine; ER = extended release. AMPH = amphetamine.
Data from Wilens et al[12]; Biederman et al[13]; Michelson et al[16]; Kelsey et al.[19]

Conclusion

ADHD can be effectively treated utilizing stimulant and nonstimulant medications. Because ADHD symptoms can cause impairment throughout the day and over the lifetime, we must utilize pharmacologic and behavioral treatments that these patients need.

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