EDITORIAL

Treatment of Attention Deficit Hyperactivity Disorder in Children

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These are controversial times for those who care for children with attention deficit hyperactivity disorder (ADHD). Class action law suits have been filed in federal courts in California and New Jersey accusing a manufacturer of methylphenidate and the American Psychiatric Association of conspiring to expand the use of this drug.[1] These suits have recently been dismissed. This is just the latest chapter in the long-running debate over the existence, diagnosis, and treatment of ADHD. Controversies relating to ADHD continue to polarize physicians, educators, caregivers, and parents of these children. There are those who believe that ADHD does not exist as a true disorder. At the other end of the spectrum are those who are too quick to make the diagnosis without an adequate patient workup. Parents can unfortunately get caught in the middle of this debate when making treatment decisions for their children.

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Several factors fuel this controversy. There has not been agreement to date within the medical and psychological communities about what ADHD is or how to most effectively treat it. The lack of a well-defined diagnostic process contributes to a situation in which ADHD is probably both over- and underdiagnosed. This situation makes it difficult to characterize any disorder or determine what the best treatment options might be. Several of these uncertainties were highlighted in the findings of a recent consensus conference convened by the National Institutes of Health (NIH). A panel of experts from scientific, medical, and psychological disciplines, plus members from the public sector met and, through a series of open forums and presentations developed a consensus statement about ADHD.[2] Several findings of this panel are relevant to a discussion of how to improve therapy for this disorder.

- There is evidence that ADHD is a valid diagnosis and that it is a disorder with broadly accepted symptoms and behaviors. It is not clear whether or not ADHD represents a qualitatively distinct behavioral syndrome, or if it is at the extreme end of a spectrum of behaviors.
- Children with ADHD experience significant impairments, which can have adverse effects on academic performance, and social and vocational success. This disorder has a profound effect on individuals, families, schools, and society.
- There is wide variation in the diagnostic approach to ADHD and there is a need for a consistent set of procedures and practice guidelines. Diagnosis currently appears to be done in an inconsistent manner, leading to over- and underdiagnosis.
- A wide variety of treatments have been used for ADHD, with psychostimulants and psychosocial interventions receiving the most research interest. Psychostimulants generally produce a greater impact on core symptoms than psychosocial approaches. However, much remains to be determined about which approach is best for which symptoms, and what the benefits of combined treatment might be.
- There is wide variation in how psychostimulants are prescribed depending on the type of specialist involved. Short-term use of these drugs appears to be safe, and there is no conclusive evidence that long-term treatment is harmful.
- A team approach involving clinicians and educators from a variety of disciplines may be a mechanism to

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remove barriers to the assessment and treatment of ADHD.

The finding of the NIH panel that there is sufficient evidence to suggest that ADHD is a valid diagnosis with an accepted constellation of symptoms is important, because parents need to be assured that their children are being treated for a bona fide disorder. Subsequent to the release of the NIH report, progress has fortunately been made on the many inconsistencies in how ADHD is diagnosed and treated. The suggestion of the NIH panel that a team approach may be the best way to overcome the problems they identified opens the door for pharmacists to become involved. But what roles can they play?

Identification and Diagnosis of ADHD

It is critical that pharmacists understand what ADHD is and how it is diagnosed to effectively participate in pharmacotherapy. ADHD produces a constellation of symptoms, some of which are more responsive to medications than others. Pharmacotherapy should be targeted at symptoms on an individual basis. The response to therapy must be monitored in as objective a manner as possible, taking into consideration the type and timing of expected medication effects. Pharmacists are in an ideal position to accomplish this.

ADHD is the most common mental disorder of childhood that pharmacists will encounter. At its core are varying degrees of inattention, impulsivity, and hyperactivity that impair functioning in at least two settings, for example, at home and in school.[3] Comorbid conditions such as anxiety, depression, learning disabilities, oppositional defiant disorder, and conduct disorder are common. ADHD results in functional impairment and is a challenge for the families, teachers, and clinicians who work with these children.

The cause of ADHD remains unclear. There is evidence to suggest that neurobiologic factors are involved such as anatomical differences in regions of the brain and alterations in neurotransmitter function.[4] The role of psychological factors in causing ADHD is not clear, but these factors may modify the presentation and course of the disorder. Most experts agree that ADHD does not simply result from poor parenting. There appears to be a developmental delay in behavioral inhibition, leading to problems in executive functions such as the ability to plan and organize behaviors, to perceive time, and to engage in and sustain goal-directed behaviors.[5] These problems are associated with inattention, impulsiveness, and hyperactivity that affect the child's ability to function. They are significant and affect family and peer relationships as well as the child's ability to perform well in school. Those working with these children quickly realize that there are substantial psychosocial implications of ADHD.

The American Academy of Child and Adolescent Psychiatry (AACAP) and, more recently, the American Academy of Pediatrics (AAP) have published guidelines for the diagnosis and evaluation of individuals suspected of having ADHD.[6,7] The AAP worked in collaboration with other organizations during this process, and their recommendations are in agreement with, and to some extent expand on those published by the AACAP. There are six recommendations in these guidelines that, if applied, can help to identify patients who meet the current criteria for ADHD. They can be summarized as follows:

1. Primary care clinicians should initiate an evaluation for ADHD when a child presents with symptoms such as inattention, hyperactivity, impulsivity, behavioral problems, or poor academic achievement.
2. The diagnosis of ADHD should be based on criteria found in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.[3]
3. During the assessment for ADHD, evidence should be obtained directly from parents or caregivers regarding core symptoms in various settings. Information and evidence should include age of onset, duration and degree of symptoms, and the effects of symptoms on function. These assessments can be made through interviews and clinical observations, and may include rating scales specifically developed for ADHD.
4. The assessment of ADHD requires evidence directly obtained from the classroom teacher or other school personnel, and the physician should review school-based test results. These assessments may include rating scales specifically developed for ADHD.
5. Children being evaluated for ADHD should also be assessed for coexisting disorders.
6. Other diagnostic tests for ADHD (e.g., brain imaging or continuous performance tasks) are not routinely indicated because the specificity and sensitivity for current tests are low.

Two important points deserve emphasis. First, the diagnosis and assessment of ADHD should include information from multiple settings. ADHD does not just occur in one setting, although its manifestations may differ depending on the demands placed on the child. An alliance between clinicians, parents, and educators is critical to this process. This requires good communication between everyone involved. Secondly, the use of assessment instruments designed specifically for ADHD can be helpful. Many of these instruments not only reliably differentiate children with symptoms of ADHD from non-ADHD children, but many of them provide scores that can be compared with baseline when assessing pharmacotherapy. Therefore, although these guidelines are primarily intended to improve the diagnosis and assessment of ADHD, they will also impact the pharmacist's ability to identify and assess effective treatment strategies.

Selection and Initiation of Pharmacotherapy

Another major finding of the NIH Consensus Panel was that there are wide variations in the types and applications of therapeutic approaches used for ADHD. Both psychosocial and pharmacotherapeutic modalities are used, with psychostimulants generally producing a greater im-

pact on core symptoms than psychosocial approaches. However, the panel concluded that much remains to be determined about which approach is best for which symptoms, and what the benefits of combined therapy might be.

Parents often ask pharmacists about the relative merits of pharmacotherapy and behavioral approaches. This is especially true now that the use of medications for childhood mental disorders is so controversial. Fortunately, data have recently become available that will help pharmacists to serve not only as information resources, but also as direct participants in the optimization of therapy.

Many clinicians have accepted a multimodal approach consisting of a combination of medication and behavioral approaches as the best treatment.[8] This approach allows therapy to be tailored to the specific needs of the patient. Small trials have suggested that there are advantages to this approach, but there has been no clear demonstration of superiority, nor has there been a clear delineation of which children will benefit most. It was clear by the beginning of the 1990s that a large-scale study was needed to answer these questions. It was against this background that the National Institute of Mental Health (NIMH) convened a national panel of experts to develop a large, prospective, long-term trial in an attempt to address some of these issues, the Multimodal Treatment of Children with ADHD (MTA) study. The results of this trial have major implications on how pharmacists can better care for their patients.

The MTA methodology required a great deal of planning. One goal was that the results had to apply to the usual clinical setting. This required a compromise between the requirements for strict scientific rigor and allowing flexibility in treatment. This process was carefully explained in a series of articles[8-10] published prior to presentation of the final results. The result was a randomized, parallel-group, open study that included four treatment groups: medication management, behavioral treatment, combined treatment, and usual community care.

It should be of particular interest to pharmacotherapists that the medication management strategy of the MTA study sought to optimize therapy.[9] The study employed a manualized, algorithmic approach using methylphenidate as the initial agent. If this was not tolerated or did not appear to work, dextroamphetamine or pemoline could be substituted. If psychostimulants did not work, imipramine could be used. There was also a mechanism built in to allow other medications to be used if approved by a cross-site psychopharmacology panel.

Medication doses were carefully determined for each patient. A fixed-dose strategy was employed with a five-week, double-blind, placebo-controlled, lead-in titration phase. Several assessment instruments were used during this phase to determine both the positive and negative effects of the medication. The child's "best dose" was determined at the end of the titration period by a panel that reviewed the data. This dose was then continued for 13 months of treatment. Further dose adjustments or medication changes were allowed. Regular-release preparations were used, and multiple daily doses of up to three times daily were allowed. This approach to medication management was used in both the medication and combined treatment groups. Children randomized to community care had the same initial testing and assessment as all other groups. Information from the workup was made available to the parents and caregivers, who then took the child to whomever they chose for follow-up. No attempt was made to influence what type of treatment they received. However, approximately 70% of these children received psychostimulant therapy in whatever way the prescriber preferred.

The study included outcomes in several domains: ADHD core symptoms, oppositional/aggressive symptoms, social skills, internalizing symptoms (anxiety, depression), parent–child relations, and academic performance.[3,8] Valid and reliable test instruments and rating scales were used in each area and produced 19 specific outcome measures. Children were assessed across settings (e.g., at home and in school), and by parents, teachers, and clinicians. In addition, classroom observations and videotaped parent–child interactions augmented the primary outcome variables. All children were assessed at baseline, and again at three, six, nine, and 14 months after starting therapy. The initial results of the MTA have been published.[11,12] The first report includes the overall findings, and the second is an evaluation of the impact of different factors on outcomes.

All of the groups showed significant improvement over the 14-month study period. The importance of this finding in relationship to behavioral therapy is often overlooked. Nearly 70% of the group receiving only behavioral therapy remained in treatment, and these children were significantly improved compared with baseline. It would be inappropriate to interpret, as some have, that behavioral therapy was not found to be effective in the MTA. This therapeutic option merely did not produce the same level of benefit as optimized pharmacotherapy. There are children whose ADHD can be managed through this approach.

Medication was found to be superior to behavioral therapy for parent and teacher ratings of inattention, and for teacher ratings of hyperactivity. Medication management and behavioral treatment did not differ significantly on any other outcomes. Combined therapy was better than behavioral therapy alone for parent and teacher ratings of inattention and for parent ratings of hyperactivity/impulsivity, oppositional behavior, and reading achievement. There were no significant differences on any outcome measures between the medication-only and combined therapy groups. Medication management and combined therapy were generally better than community care in which approximately 70% of the children received medication. The authors concluded, "For ADHD symptoms, our carefully crafted medication management was superior to behavioral treatment and to routine community care that included medication." The data support this conclusion and are in agreement with those from prior studies.

The results of the MTA raised several issues that are beyond the scope of this discussion, including what role behavioral therapy might play in treatment. However, pharmacists caring for children with ADHD should recognize

that behavioral approaches (e.g., skill development, educational interventions) can be important components of treatment, and should be familiar with referral sources.

The MTA clearly shows that pharmacotherapy will remain a primary strategy in treatment. The challenge for pharmacotherapists is to transfer the medication management strategy into usual community practice so that it can be optimized for most children. There are several ways the procedures used in the MTA can be modified and used in the community.[13] Recent reports of innovative pharmaceutical care practices illustrate how this might be accomplished.

The initiation of pharmacotherapy in the MTA trial included a rigorous dose titration phase with a placebo control under double-blind conditions. Finding the optimal dose in this way may be one factor that led to better results compared with the usual community practice. But can this type of strategy be applied in the community? This type of trial was encouraged in the past, but its use has waned in recent years. Reports[14,15] of innovative pharmaceutical care services indicate that it can be implemented in community pharmacies, and several pharmacies have recently started to offer these services to local physicians. These pharmacists compound medications and placebos in matching capsules then coordinate the trial. Also as a part of these services, pharmacists collect data from parents and teachers on drug effects and provide counseling. This type of individual trial identifies those children who truly benefit most from therapy, helps to determine optimal doses, assists in making treatment decisions, and reduces unnecessary prescriptions. In one study, >90% of parents felt the trial was worthwhile, and it caused some to become steady customers of the pharmacy.[15] Another recent report[16] also indicates that this type of individual trial was highly endorsed by parents. Even parents whose children benefited from methylphenidate during the trial, but who did not wish to have their children take it endorsed it as a factor in their decision-making process. Pharmacists are the logical team members to coordinate these efforts, and there appears to be a demand for these services.

Blinded, placebo-controlled trials are clearly labor intensive and may not be possible in many settings. However, careful titration through a dose-escalating method without the use of a placebo may still give good results.[17] Open trials with a "no treatment" period have compared well with more rigorous methods to optimize the dose. Several single-case trial designs have been used in psychological studies. One very common type is the ABAB design, in which A phases are without treatment and B phases are on treatment.[18] It is critical to have a systematic approach that includes the continuous collection of data during all phases for the design to be valid. These designs can provide an option for pharmacotherapists to more objectively assess the efficacy of a medication.

Monitoring and Modifying Pharmacotherapy

The MTA illustrated the critical role of continued follow-up in optimizing pharmacotherapy.[13] Medication effects need to be assessed across settings and at different times throughout the day. These assessments should take many factors into consideration, including the child's behavior, his or her ability to stay on task, family and peer relationships, and academic progress. Pharmacists can and do play a role in this process.[14,19]

Assessment of medication effects requires that observations from both the home and school settings are evaluated.[13] Biopharmaceutical and pharmacokinetic properties of the drugs being used are important considerations during this process. For instance, the peak effects and durations of activity of immediate-release and sustained-release methylphenidate differ, and this factor needs to be taken into account when designing a monitoring program. It is common for assessments of efficacy to differ between parents and teachers. One explanation for this is that parents usually give the drug in the morning and the child is in school when the beneficial effects are most prominent. In this situation, teachers may say the drug works, while parents may be less impressed. Pharmacotherapists can modify treatment plans by taking these differences into account.

Fortunately, there are currently several different preparations of methylphenidate available from immediate-release to long-acting formulations that allow these modifications. For instance, if a child is not covered throughout the day, additional doses of regular tablets or the new product Concerta may be useful. Alternatively, if a child requires dosing later in the day, when a short-acting product is needed, a formulation that would meet this need is available. Only a complete and ongoing assessment of medication effects can direct this process.

Similar issues apply to the monitoring of adverse effects. Several investigators[13] have found that teachers report adverse drug effects less often than parents. The reasons for this are not clear since these effects might be expected to occur at times of peak serum concentrations while the child is at school. One way to help identify problems is to have the parents start the medication during the weekend when they can observe the child.

Summary

The diagnosis and treatment of ADHD will continue in spite of the current controversy. Pharmacotherapy can be optimized, and there is a great window of opportunity for pharmacists to contribute to this process. The role of the pharmacist includes provision of patient and parent education, providing counseling about medications, assisting with the selection and initiation of pharmacotherapy, and assisting with ongoing assessment of medication effects.[14,19] Patients with ADHD deserve this type of innovative pharmaceutical care.

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