New Treatments and Approaches for Attention Deficit Hyperactivity Disorder

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This has been a very exciting year for clinical trials in child and adolescent psychiatry. Never before has there seemed to be such a concentrated frenzy of activity, with important findings from several federal and industry-sponsored initiatives coming to the fore. Some of these findings have appeared in peer-reviewed journals. Many others were presented at national meetings but have not yet been published. The long lag time between presentation and publication is well-known. However, it is particularly problematic for fields such as pediatric psychopharmacology, in which there is a high demand for new and effective treatments, and off-label prescribing is the rule for many conditions. Because of the high degree of interest in pharmacologic trials in children, and the potential impact of findings from these trials on clinical care now and in the near future, this review not only focuses on findings published in peer-reviewed articles, but also on findings from studies that were peer-reviewed for presentations at national meetings and published in abstract form this past year.

Last year's clinical trials review focused on the principal results of the Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (*ie*, the MTA Study). In head-to-head comparison, well-crafted medication treatment, given alone or in combination with a comprehensive behavioral therapy program, was superior to intensive behavioral therapy offered alone (but faded over the course of treatment), or community-standard care (including medication treatment given outside the study). This finding has received considerable attention in the past year, and rightly so. Yet, the interpretations that medication treatments are preferable for all children with attention deficit hyperactivity disorder (ADHD), and that combination treatment adds little to well-crafted pharmacotherapy (as has been reported in some periodicals), do not do justice to the richness of the study findings. This year, two special sections in the *Journal of the American Academy of Child and Adolescent Psychiatry* [1] and the *Journal of Abnormal Child Psychology* [2] presented secondary papers from the MTA that serve to extend and amplify the original intent-to-treat findings [3,4]. Conners *et al*. [5] and Swanson *et al*. [6] addressed the relative effectiveness of combined versus medication treatments in greater detail, each finding that combined treatments are superior to medication treatments when analyses that preserve power are utilized. The Conners *et al*. [5] paper used a composite measure, including symptoms of ADHD and other disorders, as well as a variety of functional outcome domains, to measure treatment response. The effect size favoring combined treatment over medication only was 0.28, certainly not robust, but statistically significant. The Swanson *et al*. [6] study examined normalization as a function of composite parent-teacher ratings of ADHD and oppositional defiant disorder (ODD) symptoms on the Swanson, Nolan, and Pelham (SNAP) rating scale. Children receiving the combined treatment were 12% more likely to have ratings in the normal range (defined here as a composite score of < 1) at the conclusion of 14 months than children who only received medication. Further, the combined treatment was associated with a considerably greater likelihood of normalization than was psychosocial treatment-only (about one third of children in the latter group were rated as normalized following treatment). Effect sizes in the Swanson *et al*. [6] study parallel those in the Conners *et al*. [5] study.

Of note, certain subgroups of children with ADHD seem particularly responsive to behavioral and combined interventions. March *et al*. [7] carefully evaluated treatment response in children with comorbid ADHD and anxiety disorders, using parent and self-report ratings on the Multidimensional Anxiety Scale for Children (MASC). Children in the comorbid group showed the greatest improvement with combined treatments, but they also seemed more likely than other ADHD children to derive benefit when behavioral therapy was given alone. Jensen *et al*. [8] also found that ADHD children with anxiety disorders seemed to do relatively better than other children with ADHD when given psychosocial interventions, whether or not medication was used. In contrast, children with ADHD with comorbid conduct problems generally required medication treatment to improve. However, children with

both anxiety disorders and disruptive behavior disorders showed considerably more improvement when treated with combined medication-psychosocial interventions. This doubly comorbid group, although most often resembling the singly comorbid disruptive behavior disorder group in terms of symptomatology [8,9] had a fairly distinctive treatment response. These findings amplify the original MTA results by indicating the importance of psychosocial interventions in treating certain subgroups of children with ADHD. In addition, they also indicate that it is vitally important to appreciate comorbidity in its full context—because children with a certain comorbidity (*eg*, anxiety disorders) may have a different symptomatic presentation and treatment response when a third disorder (*eg*, one of the disruptive behavior disorders) is also present. Interestingly, the literature on comorbidity is almost exclusively about pairs of disorders, although it is not uncommon for more than two conditions to be present.

Other key findings regarding palatability and long-term maintenance of MTA treatments received their first public presentations this year. Pelham *et al*. [10] reported on the consumer satisfaction ratings of MTA treatments. Although ratings were generally high for all interventions, families receiving a psychosocial intervention (*ie*, psychosocial only or combined treatment) expressed the highest degree of satisfaction with treatment. Further, teachers of children with ADHD who received behavioral intervention rated themselves as better able to cope with those children in the classroom setting. These findings are interesting, because satisfaction with treatment may be linked to adherence over time. Several other presentations addressed the maintenance of effects seen at 14 months. Arnold *et al*. [11] reported that the overall superiority of medication and combined treatments for ADHD and ODD symptoms persisted at 24 months, 10 months after treatment in the MTA study ended. However, as there was no attempt to maintain the original randomized treatment groups after treatment, more children were taking medication by 24 months. Also, differences in symptoms across the original treatment groups were less pronounced at 24 months than they had been at 14 months. The finding of greater improvement in the medication and combined treatment groups held for ADHD symptoms, but not ODD symptoms, after controlling for having received medication during the follow-up period. Perhaps not surprisingly, there was a relationship between treatment response and adherence to medication treatment recommendations [12]. In addition, other patterns of referral emerged, with patients tending to seek treatments as a function of their prior treatment experience, and treatment providers tending to refer to treatments with which they were the most familiar. These initial findings, which point to the continued response of patients with ADHD symptoms to medication treatments over a long term, and the impact of past treatment experience on future health-seeking behavior, are indeed provocative. But they should be understood as preliminary at this point, and subject to revision pending more definitive analyses.

As important as the MTA Study is, there was every bit as much interest this year in findings emerging from several industry-sponsored clinical trials of new treatments for ADHD. Several of the studies focused on efficacy of new, long-acting stimulant treatments, but there were also important studies of novel and existing nonstimulant medications. These treatments have been designed to ameliorate problems related to the short time duration and inconsistent absorption of previously available stimulant preparations, and to provide effective and safe non-stimulant treatment alternatives. A major event this year was the release in August, 2000 of Concerta, a new long-acting preparation of methylphenidate marketed by Alza Pharmaceuticals (Mountain View, CA). Concerta is actually a combination of immediate-release and extended-release methylphenidate. The extended-release component of the medication is offered by a novel osmotic pump delivery system. In the few months since its release, Concerta has already gained considerable popularity. Because it remains active for approximately 12 hours, Concerta obviates the need to take medication at school or work. In addition, because it is designed to be taken once daily, it offers the prospect of improving compliance with treatment, and smoothing out variations in level of function that may be seen with short-acting stimulant treatment. Finally, eliminating daytime dosing, and the need for storing medications in school and other locations, carries decreased risk of diversion of stimulants to individuals for whom they have not been prescribed.

What are the data in support of this new form of methylphenidate? Greenhill *et al*. [13] and Pelham *et al*. [14] reported that Concerta taken once daily was equivalent in efficacy to immediate release methylphenidate taken three times daily, in a large, randomized, placebo-controlled, multisite trial. Further study [15] in a laboratory setting indicated that this new preparation had a similar onset of action to the more traditional immediate release preparation, and a duration of action of 11 to 12 hours. Medication response was not significantly different in combined and primarily inattentive ADHD children [16], with both groups showing evidence of symptomatic response. However, degree of improvement in the primarily inattentive children was not superior to placebo. Importantly, gains were maintained over the course of 1 year with no change in the adverse side-effect profile [17].

Several studies examined the pharmacokinetics and efficacy of two other long-acting methylphenidate preparations currently in premarketing trials. Swanson *et al*. [18] and Spencer *et al*. [19] reported on the results of a randomized, double-blind, placebo-controlled study of 34 children who received a new modified-release preparation of Ritalin (Novartis, East Hannover, NJ). These children

showed improvement in ratings of ADHD symptoms and comportment, as well as performance on math problems at 4 to 9 hours after dosing. A different modified-release methylphenidate preparation (also not yet available) was studied in a 32-center trial, using a randomized, parallel group design [20]. Children in the medicated group showed improvement in ADHD symptoms compared with those treated with placebo. This finding was consistent across morning and afternoon rating periods, although activity likely does not last into the evening.

Shire (Florence, KY) is currently conducting premarketing studies on SLI 381, a time-release version of the mixed amphetamine salts used in Adderall. Initial findings were presented at the American Academy of Child and Adolescent Psychiatry (AACAP) meeting, indicating that the new preparation is indeed longer acting than the original Adderall formulation, and equally effective. McCracken *et al*. [21] examined the 10-mg, 20 mg, and 30-mg doses of SLI 381 in a laboratory setting, finding significant improvement over time for all of the active treatments. The 20- and 30-mg conditions were associated with the greatest improvement on both ratings and a mathematics test of vigilance. Similar to Adderall, initial effects were seen at 1.5 hours, but for SLI 381, these gains were maintained at 10.5 and 12 hours after dosing. Also in support of the long duration of action, the time of maximum concentration for SLI 381 was considerably longer than it was for Adderall [22].

Eli Lilly (Indianapolis, IN) has been conducting a series of trials in children with ADHD using the novel nonstimulant medication tomoxetine, a highly specific noradrenergic uptake inhibitor. The potential utility of a noradrenergic agent for ADHD follows from the noradrenergic hypothesis of ADHD, as well as from the initial positive experience with desipramine [23]. This year's AACAP meeting produced the first report from the initial double-blind, placebo-controlled studies of tomoxetine [24]. These data have been anticipated with interest because most clinical trials in children either test existing medications administered through a different delivery system, or agents that are currently available but labeled for other conditions or age groups. In contrast, tomoxetine is a new medication that is being studied specifically for its effects in ADHD, and primarily in children (although there are also adult studies). Children treated at 17 centers were stratified into stimulant-naive and previously stimulant-treated groups. Those in the stimulant-naive group were randomized to receive either tomoxetine, Ritalin, or placebo. Prior stimulant-treated children received either tomoxetine or placebo. Intent-to-treat analyses indicated that children in the tomoxetine group scored better on the ADHD Rating Scale (ADHD-RS) than those on placebo in both studies. Adverse side-effect profiles were generally favorable, and the magnitude of improvement and tolerability in children treated with tomoxetine was comparable with that seen in children treated with Ritalin.

Another new nonstimulant medication which is being studied in premarketing trials for ADHD is GW 320659, a mixed noradrenergic and dopaminergic uptake inhibitor currently being developed by Glaxo Wellcome (Research Triangle Park, NC). The rationale for this medication is linked to the importance of dopaminergic and noradrenergic mechanisms in the etiology and pathogenesis of ADHD, as well as the initial positive treatment experiences with bupropion [25]. Data were presented data at the AACAP annual meeting from two studies. Pharmacokinetics were evaluated in 18 7- to 12-year-old children with ADHD in a laboratory setting [26]. Response was seen at 1 hour, peaked at 3 hours, and returned to baseline by 8 hours. Clinical efficacy was evaluated in a study of 51 children treated at five centers [27]. Medication dose was sequentially titrated up to 15 mg/d, and was well tolerated. Efficacy was high; there was a 59% reduction in Conners Parent Rating Scale scores from baseline to the end of treatment, and a similar robust response on Conners Teacher Rating Scale scores.

There were also findings from several studies of treatment response in children with ADHD using medications that are currently available and approved for indications other than ADHD. Guanfacine, an α-2 adrenergic agonist similar to clonidine, but longer-acting and more specific for α-2a receptors (α-2a receptors in the prefrontal cortex are thought to regulate ADHD symptoms through their inhibitory influence on dopaminergic frontal-striatal pathways), was evaluated in a randomized, double-blind, placebo-controlled study of 34 children, 7 to 14 years old, with ADHD and tic disorders [28]. At study end, nine of 17 children treated with guanfacine were rated as much or very much improved. In contrast, none of the 17 children randomized to placebo showed improvement. Benefits were seen on the ADHD-RS and on the Yale Global Tourette Symptoms Scale. Importantly, there was no significant difference in pulse and blood pressure as a function of treatment, despite the fact that this medication was originally marketed as an anti-hypertensive agent. Horrigan and Barnhill [29] similarly found that guanfacine was well tolerated, with no appreciable change in pulse and blood pressure, in a chart review of 85 patients who were treated in their clinical psychopharmacology program.

Kotler *et al*. [30] reported on the response to venlafaxine, a currently available mixed serotonergic/noradrenergic agent, in the treatment of children and adolescents with ADHD. There have previously been studies indicating positive effects of clomipramine (also a mixed serotonergic/noradrenergic agent) in the treatment of ADHD [31], so trials with venlafaxine seem well justified. In this study, 18 children 5 to 12 years old, and 12 adolescents 13 to 17 year old were studied in a fixed-dose, open-label, parallel-group design conducted at two sites. Subjects were assigned to receive either 0.5, 1.0, or 2.0 mg/kg/d of venlafaxine, and were followed for treatment efficacy and

adverse effects. Of the 30 youth treated, 28 completed the study. Ratings improved on both the ADHD-RS and Clinical Global Impression scale as a function of treatment, with no apparent effect of dose or age of the subjects. Adverse effects were generally mild and similar to what has been reported in adults with this medication.

Hudziak *et al.* [32] examined the effects of sustained release bupropion in adolescents with ADHD. Earlier studies using the short-acting form of this medication found it to be effective [25], but the longer-acting preparation is obviously more convenient to use and presumably will be associated with improved adherence to treatment. Twenty–two adolescent responders to methylphenidate were recruited for this study. Methylphenidate was discontinued on study entry, following an assessment on the medication. Treatment with bupropion SR was initiated, first at a dose of 150 mg daily, and then at 150 mg twice daily. Findings confirmed the hypothesis that ADHD adolescents would respond at least as well to bupropion as they did to methylphenidate as it was administered in the community, and there was some suggestion of greater improvement in attention and aggressive symptoms following bupropion treatment. However, it should be noted that no attempt was made in this study to titrate the methylphenidate to an optimal dose. The conclusion of this study, that bupropion SR works as well as methylphenidate given in the community, should be tempered by our knowledge that community treatment with stimulants often falls short of the desired standard [3].

One study of considerable interest, although not a clinical trial per se, attempted to answer the question of whether stimulants have a role in the treatment of children with ADHD plus bipolar disorder, or whether they are associated with problematic adverse effects and escalation of mania. Carlson *et al.* [33,34] conducted a retrospective chart review to examine the response to stimulants in 75 6– to 12-year-old boys with ADHD, with and without comorbidity, treated at the University of Iowa in the 1970s and 1980s. Children were divided into a "maximorbid" group, consisting of children with ADHD plus symptoms of ODD, lability, emotionality, and so on, and a "minimorbid" group—those who had ADHD and less severe comorbid symptoms. Of note, there was overall improvement with stimulant treatment, and no difference in response in the two groups. Further, the maximorbid group did not generally experience an escalation of their disruptive or manic symptoms when treated with stimulants. This study provides some empirical evidence in support of treating comorbid ADHD plus bipolar (or quasi-bipolar) children with stimulants, although there are obviously caveats about the retrospective design and the fact that current assessment and diagnostic methods were not fully available when these children were diagnosed and treated.

The clinical trials discussed in this review represent only a fraction of the studies that have and are currently being conducted in the child and adolescent population (although they represent a more thorough review of newly published studies, trials with new stimulant preparations, and novel medication treatments for ADHD). The impact of these data regarding effectiveness of new treatments, and improved understanding of how to administer existing treatments, can not be overstated. We have already begun to see changes in the treatment of ADHD, following from the publication of findings from the MTA Study and introduction of new treatments such as Concerta. There will be more changes ahead as other long-acting stimulants and nonstimulants currently under development begin to reach the market. It will be interesting to contrast the clinical effects, time-action profiles, and adverse effects of the different long-acting stimulants with each other and with newer nonstimulant treatments. Most importantly, patients will benefit from having an array of options. Although this review highlights new treatments and treatment approaches for ADHD, there are many trials underway in other areas of child and adolescent psychiatry that are likely to produce equally major shifts in our level of understanding and treatment practices. We await the results of several studies in the area of mood and anxiety disorders. In particular, the RUPP (Research Units for Pediatric Psychopharmacology) study of selective serotonin reuptake inhibitor treatment of anxiety disorders in children—which was presented this year but did not appear in publication abstract form—promises to be most influential.

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