

## **Medication Treatment of AD/HD**

by Sam Goldstein, PhD

DIAGNOSES OF AD/HD ACROSS THE LIFESPAN AND MEDICATIONS to treat the condition have increased steadily and significantly in the last thirty years. Non-medical use of stimulants in adolescent and adult populations has also increased concomitantly, generating public controversy. Researchers have responded by providing scientific data generally supporting diagnostic thresholds, incidence, and appropriate treatment.



► Abikoff, H., McGough, J., Vitiello, B., McCracken, J., Davies, M., Walkup, J., Riddle, M., Oatis, M., Greenhill, L., Skrobala, A., March, J., Gammon, P., Robinson, J., Lazell, R., McMahon, D.J., & Ritz, L. (2005). Sequential pharmacotherapy for children with comorbid attentiondeficit/hyperactivity and anxiety disorders. Journal of the American Academy of Child and Adolescent Psychiatry, 44(5), 418-427. Children ages six to seventeen years

with AD/HD and anxiety were titrated to optimal methylphenidate doses and assessed along with chil-

The continued and widespread use of medication in the treatment of AD/HD, specifically stimulant preparations, is a result of both cost efficiency and a large volume of research demonstrating significant short-term positive effects. Despite their effectiveness, however, these medications have had their disadvantages. These include reports of a lack of effectiveness in a small but significant percentage of children, unwanted side effects, and a lack of consistent positive impact in improving long-term academic performance, social behavior, emotional development, and ultimately the course of the condition.

Selected from the hundreds of studies completed in the last ten years, the following studies represent a broad range of topics and issues related to medication treatment for AD/HD.

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dren who entered the study on a previously optimized stimulant. Children with improved AD/HD who remained anxious were randomly assigned to eight weeks of double-blind stimulant plus fluvoxamine or stimulant plus placebo. Of the 32 medication-naive children openly treated with methylphenidate, 81 percent improved as to AD/HD. Twenty-five children entered the randomized trial. Intentto-treat analysis indicated no differences between the stimulant plus fluvoxamine and the stimulant plus placebo groups on measures of pediatric anxiety and AD/HD symptom improvement. Medications in both groups were well tolerated. The authors concluded that children with AD/HD plus anxiety have a response rate to stimulants for AD/HD that is comparable to children with AD/HD without anxiety. They noted that the benefit of adding fluvoxamine to stimulants for anxiety remains unproven.

Adler, L.A., Spencer, T., McGough, J.J., Jiang, H., & Muniz, R. (2009). Long-term effectiveness and safety of dexmethylphenidate extended-release capsules in adult ADHD. Journal of Attention Disorders, 12(5), 449-459.

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The authors evaluated the long-term safety and effectiveness of dexmethylphenidate extended-release capsules in 170 adults with AD/HD over a six-month period following a five-week, randomized trial. The 102 adults who completed the study were assessed for AD/HD symptom improvement and medication side effects. The most common side effects, occurring in less than 15 percent of participants, were headache, insomnia, and decreased appetite. Those switched to active medication from placebo demonstrated significant improvements over placebo in AD/HD symptoms. The authors concluded from their findings that once-daily dosing of 20 to 40 mgs. Of the preparation appeared to be safe and effective for treating AD/HD in adults.

#### Adler, L.A., Spencer, T.J., Williams, D.W., Moore, R.J., & Michelson, D. (2008). Long-term, open-label safety and efficacy of atomoxetine in adults with ADHD. *Journal of Attention Disorders*, 12(3), 248-253.

This final report of a study on the safety and effectiveness of atomoxetine presented data from over four years of treatment in 384 adults with AD/HD. Significant improvements were noted in the reduction of symptoms and impairment. In this open-label study, the long-term efficacy, safety and tolerability of atomoxetine for the treatment of adult AD/HD was supported.

#### ► Barbaresi, W.J., Katusic, S.K., Colligan, R.C., Weaver, A.L., & Jacobsen, S.J. (2007). Modifiers of long-term school outcomes for children with attention-deficit/hyperactivity disorder: Does treatment with stimulant medication make a difference? Results from a population-based study. *Journal of Developmental and Behavioral Pediatrics*, 28(4), 274-287.

These authors examined the significance of potential modifiers of long-term school outcomes in 370 children with AD/HD, including those treated with stimulants, from a population-based birth cohort of 5,718 children. Analyses of data from school and medical records showed that treatment with stimulants was associated with better school outcomes-increased reading achievement, decreased absenteeism, and decreased grade retention. Longer duration of treatment was also associated with decreased absenteeism. Other potential modifiers such as socio-demographic risk, comorbid learning or psychiatric disorders and receipt of special education services were found to be associated with poorer outcomes. The authors concluded that in this birth cohort, stimulant treatment of children with AD/HD was associated with improved school outcomes, providing support for efforts to ensure that children with AD/HD receive appropriate long-term medical treatment.

Bedard, A.C., Ickowicz, A., Logan, G.D., Hogg-Johnson, S., Schachar, R., & Tannock, R. (2003). Selective inhibition

#### in children with attention-deficit hyperactivity disorder off and on stimulant medication. *Journal of Abnormal Child Psychology*, 31(3), 315-327.

Selective inhibition was assessed in a group of 59 clinic-referred children diagnosed with AD/HD compared to that of a community sample. Methylphenidate effects on selective inhibition were assessed in a subset of the AD/HD sample participating in an acute, randomized, placebo-controlled, crossover trial with three fixed doses of methylphenidate. Children with AD/HD performed more poorly than controls on the majority of selected stop-signal tasks. They exhibited more invalid responses with less accurate and more variable responses on the response execution task as well as a slower selective inhibition process. Methylphe-

### What Have We Learned?

- > Stimulant medications can help children with AD/HD even if they have co-occurring problems such as anxiety, bipolar disorder, and mental retardation.
- > Stimulant and related medications work as effectively in adults as in children.
- > Long-term use of stimulant medication to treat AD/HD is associated with better school, social, and behavioral outcomes in some studies. However, stimulant treatment is but one of a number of variables that affect outcomes for children with AD/HD.
- Stimulant medication appears to have a broad impact on functioning, including improving inhibitory and executive processes.
- Children with Combined Type AD/HD appear to show a broader improvement in functioning with medication than children with Inattentive Type AD/HD, particularly with reductions in hyperactive and aggressive behavior.
- Carefully managed stimulant medication may be more effective in symptom reduction, particularly when combined with psychosocial interventions.
- > Though long-term stimulant use can reduce growth, research suggests that for most children, the impact of stimulant treatment on final adult height is minor.
- > Stimulant medications improve the driving behavior of individuals with AD/HD.
- > Medication dosage does not necessarily need to increase as children grow older.

nidate improved speed of both inhibition and response execution processes. It also reduced variability of response execution and decreased non-selective inhibition. These results are consistent with an inhibition-deficit hypothesis for AD/HD but also suggest that neither the impairment caused by AD/HD nor methylphenidate effects themselves are restricted to inhibitory processes.

#### Carach, A., Figueroa, M., Chen, S., Ickowicz, A., & Schachar, R. (2006). Stimulant treatment over 5 years: Effects on growth. *Journal of the American Academy of Child and Adolescent Psychiatry*, 45(4), 415-421.

Appetite suppression and weight loss have long been considered side effects associated with stimulant treatment in children with AD/HD. Research findings on short- and long-term effects on height and weight have been somewhat inconsistent, however, with some studies demonstrating decrease in rate of weight gain while others demonstrate no long-term effects on ultimate adult height. In an effort to resolve some inconsistencies, data from a five-year follow-up of children in a stimulant treatment study were examined with respect to standardized weight and height data. The study generated a model using hierarchical linear modeling predicting changes in child size based on medication dosage, length of treatment, and child age. Seventy-nine children with AD/HD participated in a one-year study of stimulant treatment; 68 were followed for a full five years. When length of treatment was controlled, daily dose size was negatively associated with child height and weight. According to the generated model, doses of 1.5 mgs/kgs/day were associated with decreases in weight at all time points. For height, doses of 2.5 mgs/kgs/day and higher were associated with small but significant decreases in height only after four years of treatment. For a 13-year-old boy receiving that level of treatment, the model predicted height 1.9 centimeters below the mean. Changes in child weight and height are dependent on dose size, length of treatment, and consistency of treatment. Because common stimulant-use patterns involve breaks in treatment, the authors speculated that the impact of stimulant treatment on final adult height is negligible.

#### Chacko, A., Pelham, W.E., Gnagy, E.M., Greiner, A., Vallano, G., Bukstein, O., & Rancurello, M. (2005). Stimulant medication effects in a summer treatment program among young children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 44(3), 249-257.

Five- and six-year-old children attending a summer treatment program between 1987 and 1997 underwent a randomized, clinical assessment of the effect of two doses of methylphenidate and placebo on social behavior and academic performance. Methylphenidate had an effect on all four social behaviors and improved two of the three areas of academic functioning. Dose effects were present for three of the seven dependent measures. Individual analyses indicated the therapeutic response rate between 39 and 100 percent across dependent measures. Furthermore, analyses indicated that across several important dependent measures, 39 to 98 percent of children showed little incremental improvement with the higher dose compared with the lower dose of stimulant medication. The authors concluded that stimulant medicaStimulant and related medications work as effectively in adults as in children. Stimulant medication appears to have a broad impact on functioning, including improving inhibitory and executive processes. Carefully managed stimulant medication may be more effective in symptom reduction, particularly when combined with psychosocial interventions.

tion is an effective treatment for young children diagnosed with AD/HD. However, multiple domains of functioning must be assessed to determine the most effective dose in this age range. In this study, nearly half of the original subjects were significantly benefitted by psychosocial intervention.

#### ► Cox, D.J., Merkel, R.L., Kovatchev, B., & Seward, R. (2000). Effect of stimulant medication on driving performance of young adults with attention-deficit hyperactivity disorder: A preliminary double-blind placebo controlled trial. *Journal of Nervous and Mental Disease*, 188(4), 230-234.

A number of studies have demonstrated the relative increased risks of driving-related morbidity in adults with AD/HD. These authors examined the driving performance of seven males with AD/HD compared to six matched controls in a double-blind methylphenidate versus placebo crossover study using a driving simulator. The authors found that compared with subjects without AD/HD, those with AD/HD had more career driving accidents and motor vehicle violations. They also drove worse on the simulator under placebo conditions, demonstrated significant improvement under the methylphenidate condition, rated themselves as driving poorer during the placebo condition, and tended to perceive their driving to be better during the methylphenidate condition.

#### ► Findling, R., Short, E., McNamara, N.K., Demeter, C., Stansbery, R.J., Gracious, B.L., Whipkey, R., Manos, M.J., & Calabrese, J.R. (2007). Methylphenidate in the treatment of children and adolescents with bipolar disorder and attention-deficit/ hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46(11), 1445-1453.

A group of 5- to 15-year-olds meeting DSM-IV criteria for bipolar disorder and AD/HD receiving a stable dose of medication to treat the bipolar symptoms continued to have clinically significant symptoms of AD/HD. In a four-week, double-blind placebo controlled trial, subjects received one week each of placebo, methylphenidate 5 mgs twice daily, methylphenidate 10 mgs twice daily, and methylphenidate 15 mgs twice daily, using a full-week, crossover design. At the study's end before the blind was broken, a best-dose week for each subject was determined. Lower scores during the best-dose treatment compared to the weaker placebo treatment were found on an AD/HD rating scale suggesting a therapeutic benefit from adding methylphenidate to the treatment regimen. The combined treatment was generally well tolerated.

# ► Findling, R. L., Short, E. J., & Manos, M. J. (2001). Developmental aspects of psychostimulant treatment in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40(12), 1441–1447.

These authors examined the relationship between age and short-term clinical response to psychostimulant treatment in youth with AD/HD. In a population of 177 patients treated with either methylphenidate or mixed amphetamine salts, behavioral ratings by teachers and parents were examined for dose and medication effects. The medications had similar efficacy in children and teenagers. Older youth, however, benefitted from a smaller, weight-adjusted dose of medication, as did the younger children. The authors suggest that psychostimulants are equally effective in treating children and adolescents with AD/HD. They also suggest that adolescents with AD/HD may not necessarily require more medication than younger children to achieve a similar therapeutic response.

#### ► Gorman, E.B., Klorman, R., Thatcher, J.E., & Borgstedt, A.D. (2006). Effects of methylphenidate on subtypes of attention-deficit/ hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 45(7), 808-816.

Children with the three subtypes of AD/HD entered a six-week, double-blind trial of placebo and methylphenidate in divided doses. They received a restricted arithmetic task without medication before the trial and after their noon dose on the last day of each phase. Thirtyfour unmedicated controls were tested at comparable time points. Parents and teachers rated children with AD/HD before and after each phase of the trial. Parents rated controls before the study. Controls had marginally better arithmetic performance than children with Combined Type AD/HD, who outperformed children with Inattentive Type AD/HD. Unmedicated children with AD/HD had more taskincompatible behaviors than controls during restricted arithmetic. With methylphenidate, both AD/HD subtypes reached control levels of arithmetic performance and task-incompatible behavior. Before the trial parents rated children with AD/HD subtypes higher than controls on inattention, hyperactivity, and oppositionality/aggression. Parents and teachers also rated Combined Type children higher than Inattentive Type children on hyperactivity and oppositionality/aggression but not inattention. Methylphenidate lowered parent and teacher ratings of inattention and hyperactivity for those with all AD/HD subtypes, but ratings of children with Combined Type AD/HD decreased more in hyperactivity and aggression.

#### ▶ Pearson, D.A., Santos, C.W., Roach, J.D., Casat, C.D., Loveland, K.A., Lachear, D., Lane, D.M., Faria, L.P., & Cleveland, L.A. (2003). Treatment effects of methylphenidate on behavioral adjustment in children with mental retardation and ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry*, 42(2), 209-216.

These authors set out to determine the effects of stimulant medication in children with impaired intellect meeting the diagnostic criteria for AD/HD. Twenty-four children were evaluated during a placebo-controlled, double-blind, crossover treatment trial with methylphenidate. The results suggested that symptoms of AD/HD can be treated successfully in children with comorbid intellectual impairment and AD/HD, and as found in normal populations, higher doses are often more effective. The improvements were not accompanied by increased symptoms such as staring, social withdrawal, or anxiety.