Brain Imaging Targets ADHD Differences

By Salynn Boyles
WebMD Medical News Reviewed By Brunilda Nazario, MD
on Thursday, November 20, 2003

Nov. 20, 2003 -- A brain imaging study has pinpointed exactly where the brains of children with attention deficit hyperactivity disorder differ from those of other children. Researchers say the finding could one day lead to better drugs and behavioral interventions to treat kids with ADHD.

Earlier studies have shown that children with ADHD tend to have brains that are slightly smaller than normal, and researchers have long suspected that the disorder is caused by a dysfunction in the frontal lobes of the brain, which control emotions and impulses.

The new study, published in the Nov. 22 issue of the journal *The Lancet*, is the most detailed look at the brains of kids with attention deficit hyperactivity disorder ever undertaken.

Differences in Both Sides of Brain

Investigators at UCLA used magnetic resonance imaging (MRI) to compare the brains of 27 children with ADHD to those of 46 children without the disorder. They found that the region of the brain associated with attention and impulse control, located on the bottom of the frontal lobes of the brain, was smaller in the ADHD kids than in the other children.

"We would expect that the abnormalities would be in this region, and this is what we found," lead investigator Elizabeth Sowell, PhD, tells WebMD.

The researchers also found that children with ADHD had larger areas of the outer layers of the brain.

Previous research has indicated that the differences were limited to the right side of the brain, but Sowell and colleagues found that they occurred on both sides.

Better Treatments

Sowell says pinpointing the exact location associated with ADHD could help in the development of new drugs for the treatment of the disorder. Child psychiatrist and senior investigator Bradley S. Peterson, MD, says brain imaging may also allow clinicians to better utilize the therapies that are already in use.

"One of the next steps is to see if these brain differences are predictive of treatment responses," he tells WebMD. "I think it is reasonable to assume that this will be the case. Imaging may help us predict who is going to respond to certain kinds of treatment."

ADHD symptoms disappear with age in some children, but not others. Peterson says brain imaging may also prove useful for distinguishing between the two. He says studies to test all of these theories are planned.

SOURCES: *The Lancet*, Nov. 22, 2003, vol. 362: pp 1699-1707. Elizabeth Sowell, PhD, assistant professor of neurology, David Geffen School of Medicine, Laboratory of Neuro Imaging, UCLA. Bradley Peterson, MD, Suzanne Crosby Murphy Associate Professor of Psychiatry, Columbia University and New York State Psychiatric Institute.

Introduction to New Research: Navigating Complex Treatment Options for ADHD

Alisa Gutman

Introduction

Current thinking in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD) implicates catecholamine dysfunction as a major factor in the disease. Multiple brain regions are affected in ADHD patients; posterior parietal cortex (posterior sensory integration centers) and prefrontal cortex (anterior attention and executive function centers) are sites modulated by monoamines and considered important in symptoms associated with ADHD. Historically, treatment of ADHD has been with dopaminergic drugs. For this reason, most people believe that dopamine dysfunction is at the heart of the problem in this disorder. However, it is important to realize the "promiscuous" nature of the catecholamine systems. The norepinephrine transporter has been shown to regulate dopamine reuptake in the prefrontal cortex and is a potent agonist of the D4 dopamine receptor.[1-3] Additional interactions are found between norepinephrine and dopamine transmission, such as increases in norepinephrine release in the nucleus accumbens as a result of extrasynaptic DRD1 activation.[4]

Genetic Disorder

ADHD is a genetic disorder, with twin studies showing a mean heritability of 0.8.[5] It is now clear that ADHD is a polygenic disorder, with multiple genes implicated, including several in the catecholamine system. Dopaminergic genes preferentially transmitted to ADHD probands include the 480-bp dopamine transporter 1 (DAT1) allele and the dopamine receptor 4 (DRD4) 7-repeat allele.[6-10] Family-based studies of ADHD show a pooled odds ratio of 1.4 for association between ADHD and DRD4, as shown in a meta-analysis by Faraone and colleagues.[9] Associations have also been found with noradrenergic genes, including alpha-2a and alpha-2c receptors and dopamine beta-hydroxylase.

Anatomic Findings

On an anatomic level, total cerebral volume is approximately 3% smaller in youth with ADHD. Kim and colleagues[11] have shown reduced perfusion of bilateral orbitofrontal cortex and cerebellum in 40 children with ADHD. They also found increased perfusion of right parietal cortex and left parieto-occipital cortices in children with ADHD. Castellanos and colleagues[12] looked at brain region volume over time in children with ADHD and observed normalization of reduced caudate volume in ADHD by midadolescence. In contrast, the reduction in cerebellar volume compared with control subjects persisted through adolescence.

Imaging Studies

One of the most consistent findings in imaging data from ADHD subjects has been reduced striatal activation with inhibition tasks, such as the Go/No-Go paradigm.[13-15] In perceptual tasks, studies have shown more activation in the left caudate nucleus, left anterior cingulated gyrus, and bilateral parietal lobe in adolescents with ADHD vs controls. A study in adults with ADHD showed

a similar pattern of altered perceptual processing in which the ADHD brain failed to use the normal pathway to process data in a Counting Stroop Task. Some imaging has been done using dopaminergic ligands to observe the dopamine system in subjects with ADHD. Several studies have found increased dopamine transporter function in both children and adults with ADHD.[16-19]

Recent studies have taken advantage of positron emission topography (PET) as a tool for better understanding how ADHD drugs exert their effects in patients. This method allows researchers to observe occupancy of dopamine transporters by first giving the subject cocaine and observing the extent of displacement of this radiolabelled compound by different doses of drug.[20] A typical therapeutic dose of methylphenidate (MPH, 0.3-0.5 mg/kg) occupies more than 50% of dopamine transporters. Other studies have shown that MPH significantly increases extracellular dopamine in the human brain. Imaging studies have also been used to show efficacy of MPH treatment in ADHD subjects. An important study by Vaidya and colleagues[15] found normalization of regional brain activity when ADHD subjects were administered MPH. Several studies have shown decreased striatal dopamine transporter following MPH treatment,[19,21] and striatal DRD2 is also downregulated after treatment with MPH.[21,22]

Atomoxetine has a unique site of action from the other drugs used for ADHD. It selectively binds to and blocks the norepinephrine transporter, thereby increasing norepinephrine concentration in the synapse and effectively prolonging duration of action of this neuromodulator. Bymaster and colleagues[23] found that atomoxetine increased both norepinephrine and dopamine in the rat prefrontal cortex (the latter effect because dopamine is cleared by the norepinephrine transporter in this region). Interaction between the dopamine and norepinephrine systems is also seen with stimulant use. MPH administration increases both dopamine and norepinephrine in the rat prefrontal cortex.

New Long-Acting Preparations

In recent years, many different long-acting MPH preparations have been introduced. While all contain the same active drug, these formulations differ pharmacokinetically due to modified release technology. Pharmacokinetics refers to how the body processes a drug, including time course of drug absorption, distribution to tissues and receptors, metabolism, and excretion. Several pharmacokinetic concepts are important in understanding drug differences and therefore choosing the appropriate preparation for your patient: (1) $t_{1/2}$ = the time for drug concentration to decrease 50%; (2) area under the curve (AUC) = indication of total systemic exposure of a drug; (3) C_{max} = the maximum plasma concentration of a drug; (4) T_{max} = the time it takes to reach C_{max}; and (5) F = bioavailability.

Immediate-release MPH (dl-MPH) has a $t_{1/2}$ of 2-3.5 hours, C_{max} of 6-15 ng/mL at typical doses, T_{max} of 1.5-2.5 hours, and F of approximately 23% of the d-isomer. Twice-daily dosing of immediate-release formulations results in 2 drug peaks per day; the MPH is rapidly cleared and no drug is in the system on the following day. In an attempt to avoid the peaks and valleys that are observed with the immediate-release formulations, *Ritalin* SR was introduced. While the AUC was similar for *Ritalin* IR and *Ritalin* SR, the SR product did not provide optimal symptom relief for patients.[24]

Concerta (MPH hydrochloride) was introduced with *OROS* technology, a drug delivery system consisting of immediate- and late-release compartments with a push compartment that expands to release drug from the capsule, and was designed to have an AUC similar to 3-times-daily dosing. *Metadate* CD takes advantage of a bead drug release technology with a 30/70 mixture of immediate-release beads and extended-release beads. In a comparison between *Metadate* CD (20 mg) and *Concerta* (18 mg), Gonzalez and colleagues[25] observed similar AUC for the 2 drugs, with *Metadate* showing a higher initial peak but *Concerta* remaining elevated for a longer time

period. More recently, *Ritalin* has released *Ritalin* LA, which employs bimodal release of fast and slow release beads in a 50/50 mixture.[26]

All of the extended-release formulations discussed here are composed of a racemic mixture of d- and l-MPH. Human trials have indicated that the therapeutic activity of the racemic mixture is attributed to the d isomer,[27] including a PET study showing binding of d-MPH, but not l-MPH, to the dopamine transporter.[20] Animal studies support this notion, and even indicate that the presence of l-MPH actually diminishes the activity of d-MPH.[28] A recent study by Margaret Weiss and colleagues[29] compares Clinical Global Impression-Improvement (CGI-I) ratings between subjects administered d-MPH, dl-MPH, and placebo. *Focalin* d-MPH or dexmethylphenidate hydrochloride (the d-threo-enantiomer of racemic MPH hydrochloride, a 50-50 mixture of the d-threo and l-threo enantiomers) had better global improvement ratings, higher remission rates, longer duration of action, and lower failure rates than the racemic mixture.

Summary

While many treatments for ADHD are currently available, understanding the drugs both mechanistically and pharmacokinetically can enable clinicians to choose the appropriate therapy for their patients. Both genetic and anatomic studies implicate catecholamine pathways in the pathophysiology of this disorder. Current treatments target the dopaminergic and noradrenergic systems, and both show efficacy in clinical studies. Choosing among the many sustained-release formulations can be difficult, but each has a different pharmacologic profile. Drug peaks and valleys of the different formulations, as described here, can be matched to a patient's needs in order to achieve the highest clinical efficacy.

References

1. Cass WA, Gerhardt GA. In vivo assessment of dopamine uptake in rat medial prefrontal cortex: comparison with dorsal striatum and nucleus accumbens. J Neurochem. 1995;65:201-207. Abstract
2. Lanau F, Zenner MT, Civelli O, Hartman DS. Epinephrine and norepinephrine act as potent agonists at the recombinant human dopamine D4 receptor. J Neurochem. 1997;68:804-812. Abstract
3. Newman-Tancredi A, Audinot-Bouchez V, Gobert A, Millan MJ. Noradrenaline and adrenaline are high affinity agonists at dopamine D4 receptors. Eur J Pharmacol. 1997;319:379-383. Abstract
4. Vanderschuren LJ, Wardeh G, De Vries TJ, Mulder AH, Schoffelmeer AN. Opposing role of dopamine D1 and D2 receptors in modulation of rat nucleus accumbens noradrenaline release. J Neurosci. 1999;19:4123-4131. Abstract
5. Faraone SV. Genetics of childhood disorders: XX. ADHD, Part 4: is ADHD genetically heterogeneous? J Am Acad Child Adolesc Psychiatry. 2000;39:1455-1457.
6. Barr CL, Xu C, Kroft J, et al. Haplotype study of three polymorphisms at the dopamine transporter locus confirm linkage to attention-deficit/hyperactivity disorder. Biol Psychiatry. 2001;49:333-339. Abstract
7. Comings DE, Wu S, Chiu C, et al. Polygenic inheritance of Tourette syndrome, stuttering, attention deficit hyperactivity, conduct, and oppositional defiant disorder: the additive and subtractive effect of the three dopaminergic genes--DRD2, D beta H, and DAT1. Am J Med Genet. 1996;67:264-288. Abstract
8. Cook EH Jr, Stein MA, Krasowski MD, et al. Association of attention-deficit disorder and the dopamine transporter gene. Am J Hum Genet. 1995;56:993-998. Abstract
9. Faraone SV, Doyle AE, Mick E, Biederman J. Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. Am J Psychiatry. 2001;158:1052-1057. Abstract

10. Swanson JM, Flodman P, Kennedy J, et al. Dopamine genes and ADHD. Neurosci Biobehav Rev. 2000;24:21-25. Abstract
11. Kim BN, Lee JS, Shin MS, Cho SC, Lee DS. Regional cerebral perfusion abnormalities in attention deficit/hyperactivity disorder. Statistical parametric mapping analysis. Eur Arch Psychiatry Clin Neurosci. 2002;252:219-225. Abstract
12. Castellanos FX, Lee PP, Sharp W, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA. 2002;288:1740-1748. Abstract
13. Durston S, Tottenham NT, Thomas KM, et al. Differential patterns of striatal activation in young children with and without ADHD. Biol Psychiatry. 2003;53:871-878. Abstract
14. Rubia K, Overmeyer S, Taylor E, et al. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. Am J Psychiatry. 1999;156:891-896. Abstract
15. Vaidya CJ, Austin G, Kirkorian G, et al. Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. Proc Natl Acad Sci U S A. 1998;95:14494-14499. Abstract
16. Dougherty DD, Bonab AA, Spencer TJ, et al. Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet. 1999;354:2132-2133. Abstract
17. Cheon KA, Koo MS, Cheon KA, et al. Dopamine transporter density in the basal ganglia assessed with [123I]IPT SPET in children with attention deficit hyperactivity disorder. Eur J Nucl Med Mol Imaging. 2003;30:306-311. Abstract
18. Dresel S, Krause J, Krause KH, et al. Attention deficit hyperactivity disorder: binding of [99mTc]TRODAT-1 to the dopamine transporter before and after methylphenidate treatment. Eur J Nucl Med. 2000;27:1518-1524. Abstract
19. Krause KH, Dresel SH, Krause J, Kung HF, Tatsch K. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. Neurosci Lett. 2000;285:107-110. Abstract
20. Ding YS, Fowler JS, Volkow ND, et al. Chiral drugs: comparison of the pharmacokinetics of [11C]d-threo and L-threo-methylphenidate in the human and baboon brain. Psychopharmacology (Berl). 1997;131:71-78. Abstract
21. Vles JS, Feron FJ, Hendriksen JG, et al. Methylphenidate down-regulates the dopamine receptor and transporter system in children with attention deficit hyperkinetic disorder (ADHD). Neuropediatrics. 2003;34:77-80. Abstract
22. Ilgin N, Senol S, Gucuyener K, Gokcora N, Sener S. Is increased D2 receptor availability associated with response to stimulant medication in ADHD. Dev Med Child Neurol. 2001;43:755-760. Abstract
23. Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology. 2002;27:699-711. Abstract
24. Patrick KS, Straughn AB, Jarvi EJ, Breese GR, Meyer MC. The absorption of sustained-release methylphenidate formulations compared to an immediate-release formulation. Biopharm Drug Dispos. 1989;10:165-171. Abstract
25. Gonzalez MA, Pentikis HS, Anderl N, et al. Methylphenidate bioavailability from two extended-release formulations. Int J Clin Pharmacol Ther. 2002;40:175-184. Abstract
26. Markowitz JS, Straughn AB, Patrick KS, et al. Pharmacokinetics of methylphenidate after oral administration of two modified-release formulations in healthy adults. Clin Pharmacokinet. 2003;42:393-401. Abstract
27. Srinivas NR, Hubbard JW, Quinn D, Midha KK. Enantioselective pharmacokinetics and pharmacodynamics of dl-threo-methylphenidate in children with attention deficit hyperactivity disorder. Clin Pharmacol Ther. 1992;52:561-568. Abstract
28. Davids E, Zhang K, Tarazi FI, Baldessarini RJ. Stereoselective effects of methylphenidate on motor hyperactivity in juvenile rats induced by neonatal 6-hydroxydopamine lesioning. Psychopharmacology (Berl). 2002;160:92-98. Abstract

29. Weiss M, Murray C, Weiss G. Adults with attention-deficit/hyperactivity disorder: current concepts. J Psychiatr Pract. 2002;8:99-111.

Genetic and Phenotypic Advances in ADHD

Alisa Gutman

Research in ADHD has revealed high heritability of the disorder, and many risk factors have already been identified. Still, the nature of the risk incurred by these genes and the mode of inheritance remain largely unknown. Additional complexity arises from the fact that whatever this genetic risk is, it is not always expressed, as ADHD shows incomplete penetrance. Our understanding of ADHD and our ability to diagnose the syndrome are currently incomplete. Measurement difficulties arise from both inconsistencies among informants and the instruments used to rate ADHD symptoms. For example, one third of individuals were conferred different diagnoses using the Conners scale vs the structured interview. For this reason, the Toronto ADHD Research Team has sought to identify quantitative behavioral traits and endophenotypes for ADHD.

Endophenotypes are traits within a particular disorder that meet the following criteria: they are specific to the disorder, stable over time, familial, rare in the general population, and independent of impairment and severity. These traits are not necessarily diagnostic (they do not have to be present in every individual with the disorder), biologically plausible, heritable, quantitative, or easily administered. Endophenotypes can help to define subtypes of a particular disorder and can be used as a quantitative trait in genetic analyses of probands and families. One endophenotype that has been used for ADHD is inhibition, an executive function that allows an individual to withhold a response if circumstances change; lack of inhibition amounts to distractibility or lack of concentration and results in errors and impulsiveness. A large body of research suggests a biological rationale for lack of inhibition as an endophenotype for ADHD. Inhibitory tasks activate the prefrontal cortex and basal ganglia, regions in which the dopamine system is associated with executive functioning.

Tests of inhibitory function, such as the stop signal task, often consist of 2 concurrent tasks (a "go" task and a "stop" task) in which the subject is signaled to stop a particular response. An individual with a poor inhibitory system will have a long reaction time. This deficit has been replicated several times and is specific to ADHD. It is not highly correlated to other disorders. In addition, performance on the task improves with methylphenidate treatment.[1] Imaging studies have shown that this inhibitory task activates the prefrontal cortex and basal ganglia. Inhibition also correlates with family history such that 48.1% subjects with poor inhibition have a family history of ADHD compared with only 7.7% of normal controls.[2]

The Toronto Family Study on ADHD has been performed to determine whether this inhibitory deficit extends to siblings of ADHD probands. The authors examined differences between concordant (proband and sibling with ADHD) and discordant (proband has ADHD and sibling does not have ADHD) sibling pairs. Inhibition, as rated by the stop signal task, was higher in control subjects for both ADHD probands and their siblings. Inhibition was not correlated with any obvious confounds, such as IQ, environmental risks, or ADHD total score or subtype.

While phenotypic measures of ADHD are important for characterization and study of the syndrome, there is also a need for molecular genetic studies of the disorder. Both genome scans and candidate gene studies have been performed to locate genes that contribute to ADHD. In a genome scan, the researcher screens all of the chromosomes for linkage with markers spaced throughout the genome. Three such genome scans for ADHD have identified several possible loci

that associate with ADHD, including 16p13,[3] 17p11,[4] 15q15.1, and 7p13.[5] Candidate gene studies use a different approach to genetics in which a gene is chosen with known biological relevance to a disorder and then tracked across families with the disorder. Many candidate gene studies have been done for ADHD, with overlap in findings for the dopamine receptor D4 (DRD4), dopamine transporter 1 (DAT1), and dopamine receptor 5 (DRD5), among others.

The Toronto group has furthered this genetic research by looking for evidence of linkage in their family study of ADHD. Genes found to be associated with ADHD probands and families included DRD4, DAT1, DRD5, DRD1, serotonin receptor (5HTR) 2A, 5HTR1B, and synaptosomal associated protein of 25 kD (SNAP-25). SNAP-25 is an interesting candidate gene for ADHD due to its critical role in neurotransmitter release. Linkage was found for 2 markers in the 3' UTR of the gene by this group,[6] as well as in 3 independent samples. A mouse strain with a mutation in the SNAP-25 gene, *Coloboma*, exhibits spontaneous hyperactivity that is corrected by dextroamphetamine but not methylphenidate.[7] Of note, while the Toronto sample found increased transmission of the SNAP-25 polymorphisms to ADHD probands, a similar link was not found in a sample studied at Irvine. As the Irvine sample was selected based on a positive response to methylphenidate, it is possible that this gene may be related to MPH response.

DRD4 has also been linked to ADHD in a number of studies. In a meta-analysis of published genetic studies on ADHD, there was high statistical significance for an association based on case-control studies and a $P = .02$ for family-based studies.[8] Many possible molecular mechanisms could account for this observed association, including changes in gene expression, loss or gain of function, or functional differences in intracellular signaling. No linkage was found for polymorphisms in the promoter region of DRD4, suggesting that the pathology is not due to differences in expression of DRD4. Okuyama and colleagues[9] found that a T to C change at -521 altered transcription rate. However, no significant evidence was found for biased transmission of these 2 haplotypes. Therefore, altered transcription could not be confirmed as the mechanism by which DRD4 contributes to ADHD. Both positive and negative findings have been observed for an association between the dopamine transporter and ADHD. Barr and colleagues[10] found that a combination of changes in intron 9 and exon 9 yields a significant link between DAT and ADHD.

While the mechanisms for gene dysregulation in ADHD remain unknown, several genes have been associated with ADHD symptoms and endophenotypes. Identification of inhibition as a trait marker for ADHD spectrum behaviors will aid researchers in finding connections between genes and some of the symptoms that contribute to the syndrome of ADHD. Among the genes believed to contribute to ADHD symptomatology are several in the catecholamine system and neurotransmitter trafficking. Further research into the differing aspects of these genes in ADHD probands is needed. It is hoped this information will aid in understanding the mechanisms that underlie the pathophysiology of ADHD.

References

1. Tannock R, Schachar R, Logan G. Methylphenidate and cognitive flexibility: dissociated dose effects in hyperactive children. J Abnorm Child Psychol. 1995;23:235-266. Abstract
2. Crosbie J, Schachar R. Deficient inhibition as a marker for familial ADHD. Am J Psychiatry. 2001;158:1884-1890. Abstract
3. Smalley SL, Kustanovich V, Minassian SL, et al. Genetic linkage of attention-deficit/hyperactivity disorder on chromosome 16p13, in a region implicated in autism. Am J Hum Genet. 2002;71:959-963. Abstract
4. Ogdie MN, Macphie IL, Minassian SL, et al. A genomewide scan for attention-deficit/hyperactivity disorder in an extended sample: suggestive linkage on 17p11. Am J Hum Genet. 2003;72:1268-1279. Abstract
5. Bakker SC, van der Meulen EM, Buitelaar JK, et al. A whole-genome scan in 164 Dutch sib pairs with attention-deficit/hyperactivity disorder: suggestive evidence for linkage on chromosomes 7p and 15q. Am J Hum Genet. 2003;72:1251-1260. Abstract

6. Barr CL, Feng Y, Wigg K, et al. Identification of DNA variants in the SNAP-25 gene and linkage study of these polymorphisms and attention-deficit hyperactivity disorder. Mol Psychiatry. 2000;5:405-409. Abstract
7. Wilson MC. Coloboma mouse mutant as an animal model of hyperkinesis and attention deficit hyperactivity disorder. Neurosci Biobehav Rev. 2000;24:51-57. Abstract
8. Faraone SV, Doyle AE, Mick E, Biederman J. Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. Am J Psychiatry. 2001;158:1052-1057. Abstract
9. Okuyama Y, Ishiguro H, Toru M, Arinami T. A genetic polymorphism in the promoter region of DRD4 associated with expression and schizophrenia. Biochem Biophys Res Commun. 1999;258:292-295. Abstract
10. Barr CL, Xu C, Kroft J, et al. Haplotype study of three polymorphisms at the dopamine transporter locus confirm linkage to attention-deficit/hyperactivity disorder. Biol Psychiatry. 2001;49:333-339. Abstract

New Research in ADHD

Alisa Gutman

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is an important area of interest for clinicians and researchers. A great deal of new data is available on new approaches and new pharmacologic formulations and treatments for children, adolescents, and adults with ADHD. Some of the studies presented at the Child and Adolescent Psychiatry Annual Meeting looked at once-daily treatment and a comparison of the various medications currently used; other studies studied cognitive-behavioral treatment, brain functioning, and driving skills.

Evaluating Single Daily Dose ADHD Medication From Effect Size Evaluation

Researchers from the University of California at Irvine looked at single daily doses of ADHD medication and evaluation of effect size (ES). There have been a number of medications that are available for ADHD. Since there are individual differences in patients' responses to the various medications, it is important to understand a medication's effect on a particular patient. Since there is essentially no way to predict an individual patient's response to a particular ADHD medication, and since there are no head-to-head comparisons of the newer agents to treat ADHD, a clinician must then try to extrapolate efficacy data from the various studies to help choose a medication to use.

Investigators decided not to perform a simple calculation of ES by combining or comparing studies, since there were relatively few studies and the studies had multiple differences. Instead, in an attempt to minimize cross-study confounds, they looked at specific studies with similar designs, outcome measures, goals, and inclusion/exclusion criteria. Likert-scale changes (LCs) were examined and compared with the ESs determined.

The researchers chose a study that represented each of the ADHD medications that provided full-day single-dose coverage (10 hours or longer), and the studies were chosen from phase 3 US Food and Drug Administration registration trials, each of which has a large n, parallel-group, double-blind, multicenter design and is placebo controlled.

Results using parent and teacher ratings showed an interesting difference in ESs: *OROS* methylphenidate (MPH) (ES = 1.02), mixed AMPH salts XR (ES = 0.74), and atomoxetine (ES = 0.62) for parent ratings and *OROS* MPH (ES = 0.96), mixed AMPH salts XR (ES = 0.84), and atomoxetine (ES = 0.44) for teacher ratings. The authors concluded that these results are consistent with previous reports that there is an overall stronger effect in stimulants vs nonstimulants. They also reported that LC-rated symptom changes for nonstimulants were smaller; however, ES suggests that these small changes are stronger than is apparent, and teacher effect is smaller than parent effect in nonstimulant only. They finally suggested that these ES calculations suggest that nonstimulant treatment is "less likely to be as effective as stimulant treatment and should be positioned for trial after stimulant failure."

Study of Once-Daily Atomoxetine in the School Setting[2]

Atomoxetine, a norepinephrine reuptake inhibitor, has shown efficacy in reducing symptoms of ADHD. Other studies have assessed symptom reduction using parent rating scales, but children often exhibit different behaviors at school vs at home. This study examined the outcome of atomoxetine treatment using teacher reports of symptoms on the ADHD Rating Scale (RS) as the primary response measure. Compared with placebo, a significant reduction in ADHD RS total scores was found (P = .001). Atomoxetine showed similar rates of most adverse events to placebo, with only significant appetite reduction and somnolence arising from treatment. Results from this study are consistent with 5 previous trials using parent reports and were independent of comorbid ODD, learning disability, age, gender, or previous stimulant exposure. This extends the data from these other studies by showing efficacy in the school setting.

Using Cognitive Behavioral Therapy in Adolescents With ADHD

While cognitive behavioral therapy (CBT) shows mixed efficacy for children with ADHD, results have been promising for adult ADHD patients. This pilot study sought to evaluate efficacy in adolescents aged 14 to 18 years using improvements in the self-directedness subscale of the Temperament and Character Inventory (TCI) as the outcome measurement. Five of 6 adolescents who completed the treatment program showed an increase in self-directedness, and the participants had overall positive subjective responses to treatment (patients indicated that they enjoyed talking to someone about their experiences and appreciated learning more about their diagnosis). While the sample size is rather small (n = 6), these results suggest that CBT could be helpful in an adolescent population and support further study with a larger group.

Memory Profiles in ADHD and Prefrontal Cortical Dysfunction[4]

Deficits in executive functioning, cognitive skills regulated by the prefrontal cortex, have been associated with ADHD. Research has also shown that the prefrontal cortex plays a role in many memory tasks. This study evaluated a number of different types of memory skills in ADHD subjects, including working memory, memory for temporal order, source memory, and free recall list-learning. Boys with ADHD performed worse than controls in executive functioning and strategic memory outcome variables, but no differences were found for verbal working memory or memory for temporal order, both typically impaired in patients with prefrontal pathology. This memory profile suggests that individuals with ADHD have selective prefrontal dysfunction rather than global loss of prefrontal processes.

Treatment of Adolescents and Adults With ADHD

According to a recent study by Swanson,[5] compliance with medication is always an issue in an adolescent population, and treatment with stimulant medications, which include methylphenidate and amphetamine, typically requires multiple daily doses to maintain efficacy. Noncompliance is a particular issue in ADHD because of the frequency of treatment, coupled with the importance of

timing of doses and the long-term nature of treatment. Noncompliance can come about through inadequate supervision of those receiving medication, leading to delayed or missed doses, or through the reluctance of individuals to take medication, which is influenced by a number of factors (eg, social attitudes, pressures or worries surrounding medication use and the inconvenience of multiple daily doses). An evaluation of a long-acting formulation (*OROS* MPH) was studied in 400 subjects (264 adolescents, 136 adults) over a 9-month period in a community setting.[5a] Symptoms of ADHD often continue later in life and cause continued problems in school and work. This study found that 87.3% of patients were satisfied with treatment after 3 months of the study. Most subjects received doses of 36 mg or 54 mg, but 11% of subjects withdrew due to lack of effectiveness at the 54-mg dose, suggesting that higher doses may be appropriate in adolescent and adult populations.

Atomoxetine in Children With ADHD With Tic Disorders[6]

A significant number of patients with ADHD have a comorbid tic disorder (10% to 35%), which can be exacerbated by psychostimulants. This study looked at atomoxetine, a nonstimulant treatment for ADHD, in ADHD subjects with tic disorders to evaluate both ADHD symptom changes and changes in tic severity. Patients were assigned to either atomoxetine (n = 76) or placebo (n = 72) and evaluated with several measures, including the ADHD Rating Scale-IV Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv), Yale Global Tic Severity Scale (YGTSS), and Tic Severity Self-Report. Atomoxetine significantly decreased ADHD symptoms on the ADHDRS-IV-Parent:Inv and did not worsen tics on either scale. In fact, a trend was found toward decreased tic severity on the YGTSS. In addition, treatment was found to be safe and well tolerated in this population, with no treatment discontinuation due to exacerbation of tics.

Driving Performance of Adolescents With ADHD[7]

ADHD leads to an increased risk of accidents in children, which often translates into high risk of motor vehicle accidents during adolescence. This study employed a repeated measure crossover design with 12 adolescent males with ADHD to assess the effects of *OROS* MPH treatment on impulsive and inattentive errors while driving, as scored by a blinded rater sitting in the back seat during drives. Subjects were randomly assigned to receive either no medication or once-daily *OROS* MPH before the first test and then the opposite treatment on a test 1 week later. Inattentive driving errors were more common with no medication (P = .01). Impulsive errors were infrequent and did not increase off medication. This study demonstrates that treatment improves driving performance in adolescent males with ADHD.

This study confirms earlier studies by Cox and colleagues[7a] and Barkley and associates[7b] that describe ADHD subjects as being at higher risk for adverse driving outcomes, and when compared with placebo, methylphenidate shows improved driving performance outcomes. There are no other studies to date of other ADHD treatments and their impact on driving skills.

ADHD Self-Report Scale (Pilot ASRS) to Rate Adult ADHD Symptoms[8]

The ADHD RS is commonly used to assess ADHD symptoms in both children and adults and has been well established as a rater-administered evaluation tool for the diagnosis of ADHD. This study evaluates a self-administered version of the rating scale for use in adults. The Pilot ASRS uses a frequency rating scale, as opposed to the frequency and severity scale in the ADHD RS. In addition, the questions have been modified for an adult population. For example, the statement "Fails to give close attention to details or makes careless mistakes in schoolwork" has been replaced with "How often do you make careless mistakes when you have to work on a boring or difficult project?" The Pilot ASRS showed good reliability for the evaluation of ADHD in adults; substantial agreement was found between Pilot ASRS ratings and ADHD RS ratings.

New Research in ADHD and Dopamine Neuroimaging Studies

Although imaging research has not provided landmark or diagnostic structural lesions in ADHD, the basal ganglia, frontal cortex, and the cerebellum have been implicated in several studies. Dopamine has been considered to play a central role in ADHD. This is primarily because children's symptoms do respond to stimulants, suggesting improvement with increased levels of dopamine. More recently, genetic studies have been pointing toward abnormalities in the DAT and DAD4 receptors. Neuroimaging studies have attempted to explore differences in brain function by targeting specific neurotransmitter systems.

Dopamine Neuroimaging Studies

Many researchers are examining whether core pathology of ADHD relates to differences in dopamine activity in the brain. Radioactive ligand imaging studies have provided a more direct method of investigating brain regions associated with abnormalities in dopamine neurotransmission. Over the past several years, researchers have been using ligands to study differences in dopamine activity in ADHD using PET and SPECT technology. Most studies have been done on animals and adult humans because of the potential danger of radioactive exposure in children.

Using a specific radioligand to target the dopamine system, researchers examined differences in fluorine-18-DOPA concentrations in specific brain regions.[9] Seventeen adults with ADHD were compared with 23 healthy controls. The contrasting image results were considered to generally reflect changes in DOPA decarboxylase activity and dopamine storage. Isotope concentration suggested that there was a decrease in DOPA decarboxylase activity in the prefrontal cortex. Although differences were not noted in the striatum or midbrain, these researchers suggested that the prefrontal abnormality was the result of primary deficits in subcortical dopamine systems.

Several studies have focused on presynaptic modulation of dopamine by looking at ligands targeting the dopamine transporter (DAT). Six adults with ADHD were reported to show a 70% increase in DAT density when compared with healthy controls and corrected for age.[10] Although subjects were studied while nonmedicated, some of them had a history of stimulant medication treatment. Another study focused on 10 ADHD drug-naive adults with a SPECT ligand for DAT before and after methylphenidate treatment.[11] They found a less striking, almost 17% increase in striatal dopamine transporter in ADHD. Using the same ligand with a larger sample, this group also reported a subsequent decrease in striatal DAT binding sites with methylphenidate treatment.[12] This suggests that stimulant treatment produces long-standing changes in the dopamine system within the striatal region of the brain.

Few studies have investigated children using radioactive techniques. At the presynaptic level, investigators used SPECT to look at DAT density in the basal ganglia of ADHD drug-naive children.[13] They showed greater than 30% binding increase in striatal DAT. At the postsynaptic level, another group studied striatal dopamine D2 receptor availability in ADHD drug-naive children before and after 3 months of methylphenidate treatment.[14] They found increased DA D2 binding in children with ADHD but also showed reduced D2 availability in these children after methylphenidate treatment.

Recent studies have focused on the change of dopamine levels within the synapse.[15] The use of multiple ligands targeting dopamine pre- and postsynaptically are coupled with PET scans taken with and without methylphenidate treatment. Adults are given [(11)C]cocaine to estimate DAT occupancy and [(11)C] raclopride to estimate levels of extracellular dopamine because it targets the D2 receptor that competes with endogenous dopamine. Methylphenidate has been shown to block DAT 60% ± 11% and decrease extracellular dopamine as measured by the 16% ± 8% reduction of striatal [(11)C] raclopride binding in normal adults.

Using this technique on subjects with ADHD, an ongoing study by Volkow[16] appears to show a different data distribution for African-American adults than white adults. Given the difficulty of recruiting African-American subjects with ADHD, the sample size is still small and results were preliminary. However, this suggests the potential importance of examining ethnic differences in neurobiology, even when disorders are epidemiologically similar. Moreover, these preliminary data suggest that the adult caudate maybe more important than the putamen with methylphenidate treatment. This may be related to the role of the caudate in cognitive processes vs motor operations, since attention deficits persist and hyperactivity decreases in adulthood. Preliminary results also suggest that adults with ADHD have a blunted response to methylphenidate-induced changes in the caudate nucleus, and this may be associated with the decreased dopamine activity in ADHD. Given the inconsistent results for the level of increased DAT activity in ADHD, methodologic differences may be critical. Further in vitro as well as in vivo research needs to examine ligand differences. Differences may occur if some ligands remain at the membrane surface whereas others are internalized.

An animal model of ADHD with mice lacking the gene encoding DAT found that serotonergic rather dopaminergic neurotransmission mediated the paradoxic calming effect of psychostimulant medication on heightened locomotor activity.[17] Future studies may also explore how drugs such as atomoxetine that target the norepinephrine system interact with the dopamine system in treating ADHD. Growing evidence suggests that the pathophysiology of ADHD may be closely related to how dopamine modulates the frontostriatal pathways, but this may not be a disorder that is exclusively affected by a single neurotransmitter system.

References

1. Steinhoff KW, Wigal T, Sawnson J. Single daily dose ADHD medication treatment effect size evaluation. Program and abstracts of the American Academy of Child & Adolescent Psychiatry 50th Annual Meeting; October 14-19, 2003; Miami, Florida. Abstract A4.
2. Weiss M, Tannock R, Kratochvil C, et al. Controlled study of once-daily atomoxetine in the school setting. Program and abstracts of the American Academy of Child & Adolescent Psychiatry 50th Annual Meeting; October 14-19, 2003; Miami, Florida. Abstract C47.
3. Deng LY, Jain U. TCI self-directedness changes using cognitive behavior therapy in ADHD adolescents. Program and abstracts of the American Academy of Child & Adolescent Psychiatry 50th Annual Meeting; October 14-19, 2003; Miami, Florida. Abstract A23.
4. Schuster J, Melamed L, Greevich S. Memory profiles in ADHD: consistent with prefrontal cortical dysfunction? Program and abstracts of the American Academy of Child & Adolescent Psychiatry 50th Annual Meeting; October 14-19, 2003; Miami, Florida. Abstract A24.
5. Swanson J. Compliance with stimulants for attention-deficit/hyperactivity disorder: issues and approaches for improvement. CNS Drugs. 2003;17:117-131.
   5a. Stein MA. OROS(R) methylphenidate for treatment of adolescents and adults with ADHD from the CONCERTA(R) Community Use Study Group. Program and abstracts of the American Academy of Child & Adolescent Psychiatry 50th Annual Meeting; October 14-19, 2003; Miami, Florida. Abstract A31.
6. McCracken JT, Sallee R, Leonard HL, et al. Improvement of ADHD by atomoxetine in children with tic disorders. Program and abstracts of the American Academy of Child & Adolescent Psychiatry 50th Annual Meeting; October 14-19, 2003; Miami, Florida. Abstract B28.
7. Cox DJ, Humphrey JW, Merkel L, et al. Driving performance of ADHD adolescents OROS(R) methylphenidate. Program and abstracts of the American Academy of Child & Adolescent Psychiatry 50th Annual Meeting; October 14-19, 2003; Miami, Florida. Abstract A34.
   7a. Cox DJ, Merkel RL, Kovatchev B, Seward R. Effect of stimulant medication on driving

performance of young adults with attention-deficit hyperactivity disorder: a preliminary double-blind placebo controlled trial. J Nerv Ment Dis. 2000;188:230-234.
7b. Barkley RA, Murphy KR, Dupaul GI, Bush T. Driving in young adults with attention deficit hyperactivity disorder: knowledge, performance, adverse outcomes, and the role of executive functioning. J Int Neuropsychol Soc. 2002;8:655-672.
8. Adler LA, Spencer T, Faraone SV, et al. Validity of pilot ADHD self-report scale (Pilot ASRS) to rate adult ADHD symptoms. Program and abstracts of the American Academy of Child & Adolescent Psychiatry 50th Annual Meeting; October 14-19, 2003; Miami, Florida. Abstract A14.
9. Ernst M, Zametkin AJ, Matochik JA, Jons PH, Cohen RM. DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A [fluorine-18]fluorodopa positron emission tomographic study. J Neurosci. 1998;18:5901-5907. Abstract
10. Dougherty DD, Bonab AA, Spencer TJ, et al. Dopamine transporter density in patients with attention deficit disorder. Lancet. 1999;354:2132-2133. Abstract
11. Krause KH, Dresel SH, Krause J, et al. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. Neurosci Lett. 2000;285:107-110. Abstract
12. Dresel S, Krause J, Krause KH, et al. Attention deficit hyperactivity disorder: binding of [99mTc]TRODAT-1 to the dopamine transporter before and after methylphenidate treatment. Eur J Nucl Med. 2000;27:1518-1524. Abstract
13. Cheon KA, Ryu YH, Kim YK, et al. Dopamine transporter density in the basal ganglia assessed with [123I]IPT SPET in children with attention deficit hyperactivity disorder. Eur J Nucl Med Mol Imag. 2003;30:306-311.
14. Ilgin N, Senol S, Gucuyener K, et al. Is increased D2 receptor availability associated with response to stimulant medication in ADHD. Develop Med Child Neurol. 2001;43:755-760. Abstract
15. Volkow ND, Wang GJ, Fowler JS, et al. Relationship between blockade of dopamine transporters by oral methylphenidate and the increases in extracellular dopamine: therapeutic implications. Synapse. 2002;43:181-187. Abstract
16. Volkow ND, Newcorn J, Wang G, et al. Evidence of decreased brain dopamine function in adults with ADHD. Program and abstracts of the American Academy of Child & Adolescent Psychiatry 50th Annual Meeting; October 14-19, 2002; Miami, Florida. New Research 51B.
17. Gainetdinov RR, Wetsel WC, Jones SR, et al. Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. Science. 1999;283:397-400. Abstract