

# Role of Executive Function in ADHD

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Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder characterized by inattention, hyperactivity, and impulsivity. ADHD is commonly treated with behavioral therapy and noradrenergic and dopaminergic pharmacotherapy with psychostimulants such as methylphenidate and dextroamphetamine. Stimulants primarily have dopaminergic and noradrenergic mechanisms of action, with blockade at the dopamine transporter reducing reuptake, resulting in an increase in these neurotransmitters at the synapse. Theoretically, inattention, hyperactivity, and impulsivity in ADHD may be due to underlying executive functioning, alerting, and orienting deficits, and the nonstimulant modafinil could be beneficial in managing symptoms of ADHD by improving these components of attention that accompany wakefulness. Although modafinil exhibits a small degree of dopaminergic action by blocking the dopamine transporter, the major effect of modafinil may be attributable to neuronal activity in the hypothalamus, particularly pertaining to the recently discovered peptides hypocretin 1 and 2 (also known as orexin A and B). However, further placebo-controlled and flexible-dose studies are needed to determine the efficacy of modafinil in treating the symptoms of ADHD in children and adults.

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**A**ttention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder, characterized by inattention, hyperactivity, and impulsivity, that affects 3% to 5% of school-aged children and may persist into adulthood in some cases.<sup>1</sup> ADHD is heterogeneous, and the clinical presentation of symptoms can vary considerably. Diagnosis in children often requires not only direct observation in the clinical setting, but also observations made by parents and teachers in natural settings such as the home or school. Common treatments for ADHD include behavioral therapy and pharmacotherapy primarily with psychostimulants such as methylphenidate, dextroamphetamine, racemic amphetamine salts, and pemoline and secondarily with nonstimulants such as clonidine, bupropion and atomoxetine. No single medication is effective for all individuals with ADHD, and researchers continue to explore the effectiveness of other treatments to reduce impairment and improve functional outcomes associated with this disorder.

Recently, a new nonstimulant agent has demonstrated efficacy in improving ADHD symptoms in children and

adults.<sup>2-4</sup> Although the exact mechanism of action is not known, modafinil does not bind to dopamine, serotonin, norepinephrine, or  $\gamma$ -aminobutyric acid (GABA) receptors and does not inhibit monoamine oxidase or phosphodiesterase. Rather, it appears to operate by targeting the neuronal activity of hypocretin 1 and 2 (also known as orexin A and B) and histamine in the hypothalamus.<sup>5,6</sup> It also appears to block the dopamine transporter, demonstrating a small degree of dopaminergic action. Research has indicated that modafinil is effective in increasing wakefulness and has been a viable alternative to stimulants in the treatment of fatigue, narcolepsy, and sleepiness without the abuse potential or some of the side effects (such as anorexia and insomnia) that are associated with stimulants.<sup>7-9</sup>

Prominent theories about ADHD suggest that inattention, hyperactivity, and impulsivity may be due to underlying deficits of the components of attention, including alerting, orienting, and executive control.<sup>1,10,11</sup> Modafinil might reduce symptoms of ADHD by increasing wakefulness, which may improve these components of attention.<sup>3</sup>

## THE ATTENTION NETWORK

The study of the mechanisms and nature of attention has a long history, particularly within the field of psychology. At the turn of the 20th century, William James wrote, "Everyone knows what attention is. It is the taking possession by the mind in clear and vivid form of one out of what seem several simultaneous objects or trains of thought."<sup>12</sup>

In the more recent past, Posner and Raichle<sup>10</sup> developed a comprehensive, multi-component theory of attention, called the neuroanatomic network theory of attention,

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which has become one of the leading models used by investigators to examine component processes of attention. In their research, Posner and Raichle identified 3 attention networks—the networks of alerting, orienting, and executing or executive control.

The alerting process, according to Posner and Raichle, refers to the readiness of an individual to respond to any type of stimulus (e.g., visual, auditory, originating from any position in space). For an individual to achieve an alert state, it is assumed there must be a decrease in neural noise, which increases the signal-to-noise ratio when a stimulus occurs. An individual responds more quickly in an optimal state of alertness, for example, defined by a warning stimulus presented 500 ms to 1 second before a target stimulus.

The orienting process refers to how and to what degree an individual is prepared for a specific stimulus (e.g., visual versus auditory, from one side of space not the other). On a neuropsychological test, orienting can be measured by presenting a cue that provides information about where the stimulus may occur on a computer screen (e.g., on the right side rather than the left). Individuals can become prepared for something specific without even moving their eyes via the process of covert orienting of attention.

Executive control refers to the process of resolving conflict when 2 responses are simultaneously called for by stimuli. In the laboratory, the Stroop task is an example. The conflicting combination of a word like *red* written in green ink creates conflict when the task is to say the color of the ink (green), due to the overlearned reading response that automatically elicits the response based on the meaning of the word (red). Executive control allows for the inhibition of the overlearned response and the execution of a response that is more appropriate given the context.

The neuroanatomy and neurochemistry of the 3 attention networks are fairly well understood. The alerting mechanism appears to be related to the neurotransmitter norepinephrine and to have a neuroanatomical locus centered in the right frontal lobe. The orienting mechanism appears to be related to the neurotransmitter acetylcholine and to have a neuroanatomical locus centered in the posterior parietal lobes. The executive control network appears to be related to the neurotransmitter dopamine and to have a neuroanatomical locus in the anterior cingulate gyrus. The attention networks are organized as a cortical-striatal loop, and thus involve multiple brain regions. Effects on neurotransmitters in the caudate nucleus in the striatum (i.e., increases in dopamine due to blockade of the dopamine transporters) exert substantial effects on frontal lobe activity. In addition to the indirect activation, direct projections from dopamine neurons in the ventral tegmentum area to the lateral frontal lobe and to the cingulate gyrus also appear to be involved in frontal activation and modulation of the attentional networks.

## MECHANISMS OF ACTION AND EFFECT PROFILES OF ADHD TREATMENTS

### Conventional Approaches to Treating ADHD

For over 50 years, stimulants have been used effectively in the treatment of ADHD. At the neural level, stimulant medications are considered to be dopamine and norepinephrine agonists that increase these neurotransmitters and, by this mechanism, exert effects on behavior and cognition. The stimulant methylphenidate is the most frequently prescribed, and its mechanism of action has become apparent to researchers through positron emission tomography scans. Methylphenidate appears to act by specifically blocking the dopamine transporter, which is dense in the striatum, thereby increasing synaptic levels of dopamine and producing its therapeutic effects.<sup>13,14</sup> Methylphenidate may increase focused attention and improve performance by increasing the efficiency of the attentional networks, which have broad effects on cognition and behavior.<sup>4</sup>

However, although an increase in dopamine elicited by stimulants is thought to improve executive function, stimulants in high doses appear to impair rather than improve performance. The typical modal dose of methylphenidate for the treatment of school-aged children is approximately 10 mg per administration, with a time-to-maximum concentration (and effect) approximately 1 to 2 hours after oral administration and a half-life of 2 to 3 hours. Due to the short half-life, multiple doses per day are required for methylphenidate to produce adequate clinical effects. Since the 1990s, the modal clinical dose has typically been around 10 mg 3 times a day. This dosing regimen produces effects that are maintained across the day, characterized by peaks and valleys and an overall slightly rising serum concentration. This rise combats what was discovered and described in the late 1990s as acute tolerance, and accounts for why afternoon serum concentrations need to be higher than morning serum concentration to maintain efficacy. Dosing frequency is basically similar for all patients, even though different individuals require different doses (e.g., 5 mg 3 times a day for the low-dose responder, 10 mg 3 times a day for the middle-dose responder, and 15 mg to 20 mg 3 times a day for the high-dose responder).

Conventional treatments available for patients with ADHD also include nonpharmacologic approaches ranging from educating family members about how to cope with symptoms to more formal behavior modification interventions. Although both psychosocial and pharmacologic treatment approaches can be beneficial in treating some of the symptoms of ADHD, combining behavior modification with pharmacotherapy may be slightly more effective than using either method alone.<sup>15</sup> The Multimodal Treatment Study of Children With ADHD (MTA)<sup>15</sup> ranked treatment response for 4 common treatment strate-

**Table 1. Percentage of Subjects With an Excellent Response to Treatment<sup>a</sup>**

Treatment	Baseline N	14-Month Endpoint, %
Combination of medication and behavioral treatment	145	68
Medication alone	144	56
Behavioral therapy alone	144	34
Usual community care	146	25

<sup>a</sup>Data from Swanson et al.<sup>15</sup>

gies from most to least effective. An excellent response was defined as the score a child without ADHD would be expected to have ( $\leq 1.0$ ) on the Swanson, Nolan, and Pelham (SNAP) rating scale (Table 1).<sup>15</sup> The 4 treatment strategies, ranked in order of effectiveness, were (1) the combination of medication management with an algorithm and behavioral treatment, (2) medication management alone, (3) behavioral therapy alone, and (4) treatment usually received in the community. Of the patients in the first treatment group, 68% were excellent responders; in the second group, 56%; in the third group, 34%; and in the fourth treatment group, 25% were excellent responders. Combination treatment and medication management were found to be significantly ( $p < .001$ ) more effective than behavioral therapy alone and usual community care.<sup>15</sup> The behavioral treatment of the MTA was as good as or better than community care, even though treatment in the community included stimulant medication, although at a lower dose and frequency of administration (e.g., 5–20 mg 2 times a day) than for the medication management and combination treatment conditions of the MTA.

Overall, stimulants produce a clinically significant decrease in motor activity, an increase in attention, and a decrease in impulsive responding—the 3 areas of ADHD symptomatology—in 65% to 75% of individuals with ADHD.<sup>1</sup> Stimulants also often improve compliance with therapy, control of impulsive aggression, social interactions, and academic performance.<sup>16</sup> However, there are some disadvantages to using stimulants to treat ADHD. The primary disadvantages include the lack of continuous symptom relief (multiple daily doses were required to maintain a clinical benefit until recently when effective controlled-release formulations were developed),<sup>17</sup> the potential for abuse and difficulty acquiring refills (owing to their Schedule II status), and adverse events such as decreased appetite, delayed sleep onset, and sometimes increased anxiety, tics, or dysphoria.<sup>16</sup> Additionally, not all patients respond to stimulants and/or behavioral therapy. Therefore, although stimulants help most patients with ADHD, effective alternatives have been the subject of research.

### A Different Approach to Treating ADHD

The pharmacokinetics, pharmacodynamics, and sites of action of modafinil differ from those of stimulants.

Modafinil appears to have a beneficial effect on the symptoms of ADHD without substantially affecting the dopaminergic system. Although modafinil blocks the dopamine transporter, the consequential increases in dopamine are not dramatic, and the therapeutic effect of modafinil is not thought to be due to dopaminergic action.

Theoretically, modafinil may target neuronal activity in the hypothalamus, particularly pertaining to the recently discovered peptides hypocretin 1 and 2. This, in turn, may produce cortical activation, a process that is essential for achieving wakefulness.<sup>18,19</sup> Hypocretin neurons appear to regulate cholinergic and monoaminergic components of the ascending reticular activating system (ARAS) that are known to mediate dimensions of arousal and may regulate wake-promoter and sleep-promoter neurons in the hypothalamus. In fact, when hypocretin neurons are destroyed or malfunction, narcolepsy can occur.

Two types of arousal may exist—stimulated vigilance and normal wakefulness—and each appears to be mediated by different pathways and neurotransmitters.<sup>5,18–21</sup> Stimulated vigilance may be mediated by monoamines, dopamine, serotonin, norepinephrine, and acetylcholine via the ARAS, and normal wakefulness (internal vigilance) may be mediated by ascending histaminergic neurons arising from the tuberomammillary nucleus within the hypothalamus. The disruption of these pathways or their neurotransmitters, therefore, might result in fatigue and cognitive dysfunction. Although stimulants have been successful in treating narcolepsy, they may activate both arousal systems, and at high doses may cause motor stereotypy, anxiety, jitteriness, and overconfidence. This may be due to overactivation of the stimulated vigilance system. In contrast, modafinil may compensate for disruptions in hypocretin signaling by acting on specific neurotransmitters (particularly histamine) within these neuroanatomical systems that activate internal (rather than stimulated) vigilance. Therefore modafinil may potentially treat symptoms, including decreased alertness and executive control, without causing undesirable hyperarousal.

Modafinil has a rapid onset of action, with a time-to-maximum serum concentration that is about the same as methylphenidate (approximately 1.5 to 2 hours). However, the half-life of modafinil (possibly 10 to 15 hours) is thought to be 3 to 5 times longer than that of methylphenidate, which has an average half-life of only 2 to 3 hours. Although modafinil has an onset of action that is related to the peak concentration, its therapeutic effect does not appear to have a duration that is equal to its half-life. A single daily dose of modafinil may have effects that occur within 1 to 2 hours of ingestion, but these effects subsequently dissipate over the next several hours at a much quicker rate than the fall in the serum concentration of the drug. Nonetheless, the duration of effects with modafinil appears to be longer than that of stimulants, which could

be advantageous for children and adults who typically must take multiple doses of immediate-release formulations of stimulants to maintain effects throughout the day.

Studies<sup>2,3</sup> of modafinil have been conducted in patients with ADHD, and considerable attention has been paid to its effects on executive control, which might be deficient in the clinical disorder. Although researchers have reported its effects of reducing inattention, overactivity, and impulsivity, much of the published research to date has been primarily uncontrolled or pilot studies. The drawback to these types of studies, in general, is that they can produce inflated effect sizes that are determined to be erroneous by subsequent controlled studies of the agent; therefore, the same caution is warranted for the interpretation of these studies.

In an open-label study, Rugino and Copley<sup>2</sup> examined the effect of a single daily dose of modafinil on clinical features of ADHD in children aged 5 to 15 years. Scores on the Conners Parent and Teacher Rating Scale-Revised (CPRS and CTRS), the ADHD Rating Scale-IV, and the Test of Variables of Attention (TOVA) were compared in children diagnosed with ADHD before and after they received modafinil treatment. Participants were given individualized doses of modafinil up to 400 mg/day for about 5 weeks. Of the 15 participants who entered the study, 11 completed the study. Based on 2-tailed paired *t* tests, TOVA scores improved by 2.43 standard deviations ( $p = .0009$ ); CTRS and CPRS index *t* scores improved by an average of 14.1 ( $p = .0009$ ) and 17.7 points ( $p = .001$ ), respectively; and mean ADHD Rating Scale-IV scores improved from the 88th percentile to the 75th percentile ( $p = .047$ ). Side effects were generally mild and responded to adjustments in treatment dose. Investigators concluded that although modafinil appeared to be helpful in treating children with ADHD, further studies using double-blind, placebo-controlled designs were needed.

A multisite, placebo-controlled study<sup>23</sup> showed substantial reductions in hyperactivity, inattention, and impulsivity in children given modafinil for ADHD. In this study, 3 variations of a total daily dose of 300 mg of modafinil were compared. Participants were given 100 mg in the morning and a mid-day dose of 200 mg; 200 mg in the morning and a mid-day dose of 100 mg; or a single 300-mg dose in the morning. The 200-mg dose of modafinil in the morning and 100 mg at noon produced the most dramatic improvements. Patients in this treatment group demonstrated the largest decrease in inattention and hyperactive-impulsive symptoms according to both teacher and parent ratings. The effect size was large for both inattention symptoms and hyperactive-impulsive symptoms, which further validated findings from open-label modafinil studies that have reported clinically significant effects in treating ADHD symptoms.

In a randomized, double-blind crossover study<sup>3</sup> of 22 adults with ADHD, modafinil (average dose of 206.8

mg/day  $\pm$  84.9) was compared with placebo on various measures. There was a dramatic decrease in ADHD symptoms but little effect on the Stroop Color-Word Test, the classic task associated with executive function.<sup>22</sup> The investigators concluded that modafinil may be a viable alternative to conventional stimulants for the treatment of adults with ADHD.

Turner et al.<sup>4</sup> conducted a double-blind, placebo-controlled study of modafinil in 60 healthy (non-ADHD) adult volunteers using a comprehensive battery of neuropsychological tests to assess its cognitive-enhancing effects. In a crossover design, participants were given daily doses of 100 mg of modafinil, 200 mg of modafinil, or placebo prior to performing a variety of tests that were designed to measure memory and attention. The profile of cognitive effects on this battery had been established for methylphenidate in the past,<sup>24</sup> allowing for a comparison between methylphenidate and modafinil. Physiologic as well as cognitive effects were measured. The stop-signal reaction task revealed an improved ability to inhibit an initiated response (i.e., a shorter stop-signal reaction time) in the 200-mg group, and thus demonstrated a dose-dependent response. Modafinil was also associated with enhanced performance over placebo on tests of digit span, visual pattern recognition memory, and spatial planning, as well as on delayed matching to sample and decision-making tasks. On the 4-choice delayed matching to sample task, there was a dramatically longer latency to response, which might be related to reflective thinking before responding. On this task, the effect was observed on the low, 100-mg/day dose, as well as the 200-mg/day dose, and no difference between the 2 doses of modafinil was noted. This is somewhat surprising since the study was conducted with the typical doses of modafinil given for wakefulness (100–200 mg/day), which are considered to be relatively low.

## SUMMARY

At the neural level, stimulant medications primarily act as dopamine and norepinephrine agonists. Although stimulants have been used effectively in the treatment of ADHD, high doses that result in an excessive increase in these neurotransmitters may be responsible for the adverse events such as delayed sleep onset and anxiety, tics, or dysphoria that often occur with these medications.

Modafinil is a nondopaminergic agent that in open-label and controlled studies has demonstrated some success in treating ADHD symptoms, possibly due to its effect on component processes of attention, executive control and alerting, which may underlie these symptoms. However, despite apparent reductions in the 3 symptom domains of ADHD—inattention, hyperactivity, and impulsivity—the specific effects of modafinil on cognition are uncertain, and more studies are needed. Additionally,

further research examining the effects of modafinil on ADHD should use flexible titration methods to optimize the dose for each subject instead of using the same dose for all subjects. Fixed-dose studies make it difficult to interpret whether some nonresponsive individuals might respond to higher or lower doses. If individual titration is exercised, then patients may be tested on optimal clinical doses. This may provide a better design with which to evaluate effects on executive control by determining the maximum effects instead of average effects for a given dose. Also, the laboratory school could be applied in investigations of modafinil to track the pharmacodynamic response over time by testing every hour after the peak effect is achieved. Tracking response might aid researchers in understanding how the mechanisms of executive control and alerting are affected and whether once-a-day dosing is sufficient to produce and maintain the optimal effect throughout the day. More placebo-controlled studies are also needed to assess the efficacy of modafinil in treating the symptoms of ADHD in children and adults.

*Drug names:* atomoxetine (Strattera), bupropion (Wellbutrin and others), clonidine (Catapres and others), dextroamphetamine (Dexedrine, Dextrostat, and others), methylphenidate (Ritalin, Focalin, and others), mixed amphetamine salts (Adderall and others), modafinil (Provigil), pemoline (Cylert).

*Disclosure of off-label usage:* The author of this article has determined that, to the best of his knowledge, modafinil is not approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder.

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