

# Mechanism of Action of Agents Used in Attention-Deficit/Hyperactivity Disorder

Timothy E. Wilens, M.D.

Several medications have been demonstrated effective in treating individuals with attention-deficit/hyperactivity disorder (ADHD). There appears to be some commonality in the physiologic mechanisms of action of these agents relevant to the treatment of ADHD. Either direct or indirect attenuation of dopamine and norepinephrine neurotransmission appears related to both the stimulant and nonstimulant medications efficacious in ADHD. However, important differences exist both between and within the specific classes of agents. Elucidating the various mechanisms of action of ADHD medications may lead to better choices in matching potential response to the characteristics (e.g., genotype) of individuals. *(J Clin Psychiatry 2006;67[suppl 8]:32-37)*

**A**ttention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder affecting children and adolescents, with persistence into adulthood.<sup>1</sup> Neurobiological studies highlight that dysregulation of largely dopaminergic and noradrenergic systems in the brain stem, striatum, cerebellum, and frontocortical regions appear operant in ADHD. Multisite studies<sup>2</sup> have highlighted the fundamental importance of medications in the management of ADHD. The medications most commonly used for ADHD include the stimulants methylphenidate (MPH) and amphetamine (AMPH), followed by the nonstimulants, including atomoxetine, catecholaminergic antidepressants,  $\alpha$ -agonists, and more recently described agents such as modafinil and nicotinic agonists.

## STIMULANTS

Efficacy for ADHD appears related to the pharmacokinetics of the medications, which in turn is related to their pharmacodynamics.<sup>3-5</sup> For example, using a simulated laboratory classroom, Swanson et al.<sup>3,6</sup> demonstrated that

an ascending release and blood concentration of MPH was necessary to optimize ADHD responsiveness throughout the day. In contrast, a flat MPH dosing regimen lost about 40% of its efficacy in the afternoon.<sup>6</sup>

While not entirely sufficient, alteration in dopaminergic and noradrenergic function appears necessary for clinical efficacy of the stimulants in ADHD.<sup>7,8</sup> Two major processes are related to the concentration of dopamine (DA) in the synapse. The more prominent and well-studied process is the exocytic release of DA and other neurotransmitters that is impulse-dependent, related largely to the potassium gradient across the cell membrane.<sup>9</sup> Through the formation of an action potential by membrane depolarization, vesicular DA is released into the synapse by exocytosis. In this manner, vesicular DA release is modulated by presynaptic receptors, while being less sensitive to agents affecting the transmembrane protein transporter.<sup>10</sup> Conversely, carrier-mediated transport of catecholamines such as DA appears operant in raising synaptic concentrations of neurotransmitters secondary to AMPH.<sup>10,11</sup> Although less is known about parallel systems in the noradrenergic system, data suggest that this system may be sensitive particularly to the various isomers of stimulants.

Release, uptake, and enzymatic inactivation of transmitters are 3 fundamental processes underlying the mechanisms of action of stimulants at the neuronal level. Preclinical studies have shown that the stimulants block the reuptake of DA and NE into the presynaptic neuron and that these drugs increase the release of these monoamines into the extraneuronal space.<sup>9,10,12-15</sup> Both the releasing AMPH and uptake-inhibiting actions of MPH and AMPH and related compounds are mediated by the catecholamine uptake transporter, which has been studied for over 40 years.<sup>9-11,16</sup> Although the DA transporter protein normally moves DA from the synapse into the cell, in the presence

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*From the Pediatric Psychopharmacology Unit, Massachusetts General Hospital, Harvard Medical School, Boston.*

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*Corresponding author and reprints: Timothy E. Wilens, M.D., Pediatric Psychopharmacology Unit, Massachusetts General Hospital; YAW 6A, 32 Fruit St., Boston MA 02114 (e-mail: twilens@partners.org).*

of AMPH the direction of transport appears to be reversed, with DA being released into the synapse.<sup>9-11</sup> Amphetamine is thought to bind to the DA transporter protein on the outside of the cell membrane, “blocking” DA reuptake back into the cell.<sup>9</sup> Amphetamine then moves into the cell, where it exchanges with DA via the DA transporter protein.<sup>9,10</sup> Cytoplasmic DA is “exchanged” from the interior of the cell to outside the cell via the sodium-dependent transport protein that can be blocked by DA reuptake inhibitors.<sup>9,10,16</sup> In this manner, extracellular AMPH is exchanged with DA, thus increasing the concentration of synaptic DA.

Methylphenidate, in contrast, primarily increases synaptic DA through a more specific interaction with the DA transporter protein, leading to specific DA reuptake blockade.<sup>9,17</sup> The stimulants bind to the DA transporter protein, with resultant inhibition of DA reuptake presynaptically.<sup>17</sup> Whereas MPH binds to the DA transport protein in a manner similar to other sympathomimetic amines, such as cocaine,<sup>17,18</sup> the slower uptake and clearance of MPH appear to be related to differences in the intrasynaptic DA concentration and ultimately its lower abuse liability.<sup>18</sup> The rate of uptake into the striatum and the association and dissociation from the DA transporter also affect the increase and absolute amount of DA in the synaptic cleft.<sup>19</sup> The degree of reuptake inhibition, baseline stimulation, and the environment (salience) appear to influence DA levels in MPH-receiving individuals.<sup>20</sup> Although apparently less important in the facilitation of neurotransmission by the stimulants, there is evidence that stimulants may also directly affect DA presynaptic inhibitory autoreceptors.<sup>21</sup>

It is of interest that one study has shown that genetic manipulation resulting in elimination of the DA transporter protein (“knockout”) leads to a virtual behavioral and pharmacologic insensitivity to MPH or cocaine in mice.<sup>22</sup> In addition, one protein, the SNAP 25 that is responsible for action-potential-related migration of presynaptic catecholamine vesicles, when altered, results in a lack of MPH responsivity.<sup>23</sup> These findings support the importance of the DA transporter protein and release mechanisms in mediating the pharmacologic and psychological response to the MPH and AMPH classes of agents while also linking response to a specific gene or gene combinations.

The role of the various enantiomers of MPH has been studied over the past decade, with recent interest in immediate and extended-release *d*-isomers of MPH.<sup>24</sup> Methylphenidate as a secondary amine gives rise to 4 optical isomers: *d*- and *l*-threo and *d*- and *l*-erythro.<sup>25,26</sup> Methylphenidate was originally produced as an 80% *d,l*-erythro and 20% *d,l*-threo compound, but it was found that the central stimulant activity resides in the threo racemate; therefore, the erythro isomer was discontinued from the standard preparation.<sup>26</sup> One commercially available preparation, in both immediate- and extended-release forms of MPH, includes only the *d*-MPH racemate. Methylphenidate is metabolized predominately by hy-

drolysis in the intestinal wall before reaching systemic circulation. In general, with the administration of racemic MPH orally, substantially more *d*-MPH relative to *l*-MPH is measurable in the serum,<sup>26-28</sup> although transdermal application of *d,l*-MPH results in appreciable concentration of both the *d*- and *l*-isomer. There may be stereoselectivity, including receptor site binding and its relationship to response, in the compounds formed.<sup>25,27</sup> In rats, the *d*-MPH isomer showed greater induction of locomotor activity and reuptake inhibition of labeled DA and NE than the *l*-isomer.<sup>29,30</sup> The *d*-isomer of MPH continues to harbor the bulk of clinical efficacy of the compound, with the possibility that *l*-MPH may compete with *d*-MPH for uptake and striatal binding.<sup>25,29,30</sup>

A proposed model to explain the effects of stimulants in ADHD includes the inhibitory influences of frontal cortical activity, predominantly noradrenergic, acting on lower (striatal) structures that are related to direct DA agonists.<sup>7</sup> Contemporary support of this notion includes preclinical work by Arnsten and Li,<sup>32</sup> demonstrating important effects of stimulants on prefrontal cortex (PFC).

Work indicates that the stimulants affect not only DA but also NE.<sup>16,31</sup> For instance, Markowitz et al.<sup>31</sup> recently reported high levels of in vitro binding of MPH at the NE transporter that was, interestingly, preferential for the *d*- versus *l*-isomer. Yet, whereas the striatum is rich in DA transporter, a paucity of NE transporters exist in the striatum proper.<sup>32</sup> In contrast, the PFC, a brain region consistently implicated in ADHD, is rich in NE.<sup>32</sup>  $\alpha_{2A}$ -Adrenoceptors are located both presynaptically and postsynaptically on NE neurons. As recently reviewed by Arnsten and Li,<sup>32</sup> DA works mainly via the D<sub>1</sub> receptor, which is rich in the PFC (and is stimulated by the stimulants). Less is known about the distribution and role of the D<sub>2</sub>-D<sub>4</sub> receptors in the PFC, although the D<sub>4</sub> receptor also has affinity for NE. Rat models suggest that MPH at “lower therapeutic doses” stimulates NE  $\alpha_{2A}$ , resulting in improved frontal lobe functioning.<sup>33</sup>

Hence, while much is known about the mechanism of action of stimulants, ongoing work will shed important information on physiologic and clinical differences between stimulant classes and enantiomers, effects on both DA and NE, and the pharmacokinetic and pharmacodynamic relationships of different stimulant preparations.

## PREDOMINATELY NORADRENERGIC AGENTS

A dysregulation of the central noradrenergic network has long been hypothesized to be an important aspect of the pathophysiology of ADHD.<sup>34,35</sup> The noradrenergic system has been intimately associated with the modulation of higher cortical functions including attention, alertness, and vigilance. As reviewed by Solanto,<sup>36</sup> preclinical and clinical research has implicated the noradrenergic effects of stimulants as important therapeutic mechanisms on en-

hancing capacities such as delayed responding, working memory, and attention. Furthermore, executive function and noradrenergic activation are known to profoundly affect the performance of attention, especially the maintenance of arousal, the ability to sustain attention on a subject, particularly a “boring” one. Moreover, attention and vigilance depend on adequate modulation by catecholamine neurotransmitters of PFC, cingulate and parietal cortices, thalamus, striatum, and hippocampus, brain networks with known high distribution of noradrenergic neurons.

### Atomoxetine

The only nonstimulant agent approved by the U.S. Food and Drug Administration for the treatment of ADHD is atomoxetine. Atomoxetine has been evaluated and shown effective in children, adolescents, and adults with ADHD.<sup>37,38</sup> Atomoxetine specifically inhibits presynaptic NE reuptake, resulting similarly in increased synaptic NE.<sup>39</sup> Atomoxetine exhibits little effect on serotonin reuptake and has minimal affinity for other receptors, neurotransmitters, or transporters.

Because of its effects on NE, it is speculated that atomoxetine influences the posterior attentional systems that may result in disengagement from stimuli and the anterior attentional systems that include the analysis of data and response preparation.<sup>39,40</sup> Unfortunately, although data on the relationship of DA to the DA transporter are abundant, few data are available on ligands with specific binding to the noradrenergic presynaptic vesicular reuptake protein. Despite the prominent effects of atomoxetine on NE reuptake inhibition, preclinical data also show that effects on noradrenergic neurotransmission may have downstream effects on DA. For example, Bymaster et al.<sup>39</sup> demonstrated increases in DA in the PFC of rats treated with atomoxetine. In contrast to stimulants, atomoxetine does not increase DA availability in the nucleus accumbens (resulting in lack of euphoria or abuse liability) and the striatum (resulting in absence of motor or tic activity). Interestingly, atomoxetine substantially increases DA in the PFC, an action that may be related to the improvements in executive and other cognitive functioning. It is speculated that stimulation of noradrenergic neuron cell bodies in the brain stem may result in direct activation of the mesencephalic-frontal connections subsequently affecting PFC activity. Hence, it is no surprise that, given the redundancy in the DA/NE systems, stimulation of NE results in increased synaptic DA in the PFC. Moreover, our difficulty in imaging the nuclei of the cell bodies originating in the ependymal areas of the brain stem has limited our understanding of direct stimulation of these areas on higher cortical functions relative to ADHD.

### $\alpha$ -Agonists (Clonidine and Guanfacine)

The antihypertensive medication clonidine has achieved an increasing prominence for the treatment of ADHD, tics,

and aggression,<sup>41</sup> particularly in younger children. Guanfacine has been demonstrated to be effective in ADHD plus tics, with outcome reported in both ADHD and tics.<sup>42</sup>

Clonidine, an imidazoline derivative with  $\alpha$ -adrenergic agonist properties, has been primarily used in the treatment of hypertension in adults. Clonidine has both central and peripheral effects.<sup>43</sup> Clonidine has high potency for central autonomic pathways that is apparently related to its hypertensive and antiwithdrawal properties. Clonidine affects both  $\alpha_1$  and  $\alpha_2$  receptors. Both  $\alpha_1$  and  $\alpha_2$  receptor types are located postsynaptically, with the  $\alpha_2$  also being located presynaptically and acting as an autoreceptor release modulator. Of note, an older literature indicates only a presynaptic location of the  $\alpha_2$  receptor, whereas important findings of the geographic location of the receptor, along with its important effects postsynaptically, have been elucidated. (For review see Arnsten and Li<sup>32</sup> and Scahill et al.<sup>42</sup>) Most effects of clonidine are centrally, as opposed to peripherally, based. Clonidine appears to block the release of NE from central catecholaminergic nerve terminals. Clonidine also reduces the turnover rate of NE, largely through its effects on the  $\alpha_2$  receptors. At least 3 subtypes of  $\alpha_2$  receptors relevant to the mechanism of action of clonidine are evident:  $\alpha_{2A}$ ,  $\alpha_{2B}$ , and  $\alpha_{2C}$ .  $\alpha_{2A}$  Receptors are predominate in the PFC, an important area of drug action relative to ADHD.<sup>44</sup>

Clonidine appears to have inhibitory effects on both catecholamine release and postsynaptic activation. For instance, preclinical animal work indicates that stimulation of postsynaptic  $\alpha_{2A}$  receptors increases blood flow in the PFC.<sup>33</sup> Likewise, using clonidine appears to improve neuropsychological functioning in the PFC as determined using simple neuropsychological tests.<sup>32</sup>

More recent work emphasizes that the effects of clonidine appear to be related to baseline and “stress” effects on the noradrenergic system.<sup>33</sup> The inhibitory effects of clonidine on neurotransmitter systems are generally modulatory; its effectiveness in inhibiting transmitter release appears frequency dependent. The modulatory ability of clonidine may allow for a more subtle degree of regulation. For instance, at very low doses, clonidine may preferentially stimulate inhibitory, presynaptic  $\alpha_2$  autoreceptors in the central nervous system.

Clonidine also interacts with a multitude of neurotransmitter systems, including catecholamines, indolamines, cholinergic ( $\alpha_2$  receptors on parasympathetic neurons), opioidergic, and amino acid systems. Such widespread neurotransmission involvement may account for its diverse action on drug withdrawal states, impulsivity, and cognition.<sup>41,43</sup> The common link may be the mediation of its actions through stimulation of  $\alpha_2$ -adrenergic receptors. Clonidine may also be involved in attenuation of the noradrenergic imidazole receptor action.

The effects of guanfacine parallel those of clonidine centrally. Guanfacine is a potent agonist of the  $\alpha_{2A}$  receptor and as such mimics NE at  $\alpha_{2A}$  receptors. In turn, activation

of the  $\alpha_{2A}$  receptor in preclinical studies results in heightened PFC blood flow and functioning (affecting working memory and executive functioning)<sup>32</sup> relevant to ADHD. Interestingly, in contrast, using these same models, agents that act as antagonists at the  $\alpha_{2A}$  receptor *worsen* PFC functioning.

In summary, both clonidine and guanfacine share important features that modulate both presynaptic and postsynaptic NE activity that appears related to basal adrenergic tone. Animal studies indicate that both agents induce important physiologic effects on the PFC, resulting in improved neuropsychological functioning relevant to the pathophysiology and treatment of ADHD.

### Bupropion

Bupropion is a novel aminoketone antidepressant related to the phenylisopropylamines and pharmacologically distinct from available antidepressants.<sup>45</sup> Preclinical data indicate that the mechanism of action of bupropion most likely involves reuptake inhibition of DA and NE.<sup>45</sup> As part of its mechanism of action, bupropion has been shown to potentiate dopaminergic neurotransmission.<sup>45</sup> Clinical research and studies of the human DA, NE, and serotonin transporters extend the preclinical findings and confirm that bupropion is a dual NE and DA reuptake inhibitor in humans at clinically relevant doses, with few data suggesting appreciable indoleamine involvement.

### Tricyclic Antidepressants

The tricyclic antidepressants have been demonstrated effective in studies of both children and adults with ADHD. A rich literature indicates the effects of tricyclic antidepressants in ADHD relative to their noradrenergic properties. (For review, see Biederman and Spencer.<sup>35</sup>) While the tertiary amines (imipramine and amitriptyline) are more selective for the serotonin transporter than they are for the NE transporter (ratio of the equilibrium dissociation constants at human monoamine transporters ranges from 8 to 27), the secondary amines (desipramine, nortriptyline, and protriptyline) are more selective for the NE transporter than they are for the serotonin transporter (ratio of the equilibrium dissociation constants ranges from 4 to 21).<sup>46</sup> Although the tricyclic antidepressants affect histaminergic and cholinergic receptors, it is assumed that the activity of the tricyclic antidepressants in ADHD stems from their actions on catecholamine reuptake, particularly that of NE. Because the tricyclic antidepressants act on many of the same sites as the stimulants, the pharmacodynamic effects of the tricyclic antidepressants may be additive to those of the stimulants or may act synergistically with the effects of stimulants.

### Modafinil

Modafinil is a nonstimulant medication used in the treatment of narcolepsy. Treatment with modafinil has

been found to result in clinically significant improvements within the parameters commonly used to assess ADHD.<sup>47</sup> Recently completed trials have shown efficacy in children with ADHD.<sup>48,49</sup>

Interestingly, despite documented efficacy, the precise mechanism or areas of action of modafinil in relation to the treatment of ADHD is not fully understood. Modafinil seems to exert one of its main effects on the hypothalamus and attenuate both cholinergic and monoaminergic components of the ascending reticular activating system. However, it does have effects on catecholaminergic neurotransmission—in particular, dopaminergic and noradrenergic systems—although whether these effects are related to modafinil's therapeutic effects in ADHD remains controversial.<sup>48</sup>

Hou et al.<sup>50</sup> found that modafinil has 4 distinct effects on the brain. It inhibits  $\gamma$ -aminobutyric acid (GABA)-producing neurons in the ventrolateral preoptic nucleus (VLPO). In turn, the VLPO normally inhibits the locus ceruleus (site of noradrenergic cell bodies) and the tuberomammillary nucleus (histamine neurons) in a resting or sleeping state. The resulting inhibition of inhibition activates noradrenergic neurons of the locus ceruleus and the histamine neurons of the tuberomammillary nucleus, leading to a more "wakeful state." In addition, the mesencephalic dopaminergic neurons are activated.

Wisor and Eriksson<sup>51</sup> looked more closely at the effects of modafinil on the dopaminergic system and found that modafinil activates the postsynaptic  $\alpha_1$ -adrenergic receptor by blocking the reuptake of DA in the cerebral cortex and caudate. This activation of adrenergic systems occurs in diffuse brain regions including the basal forebrain, cholinergic complex, cerebral cortex, and thalamus. In preclinical studies, tuberomammillary neurons and neurons of the prefrontal area were very active and ventrolateral preoptic neurons were inactive in the brains of rats after modafinil had been administered to them.<sup>52</sup> Additionally, modafinil resulted in a dose-dependent increase of orexin, which is involved in the activation of the locus ceruleus.<sup>52</sup> Moreover, this effect may also be responsible for increased histamine levels, subsequently increasing the wakefulness associated with modafinil. The more indirect effects on the catecholaminergic system have been speculated to be related to the anti-ADHD effect without the "classic" stimulant-like adverse events.<sup>53</sup> Clearly, further studies, such as ligand-based positron emission and functional neuroimaging studies in individuals with ADHD, will assist in highlighting a more precise mechanism of action and identifying specific brain regions affected with modafinil treatment.

### Nicotinic Agents

Evidence has accumulated in recent years suggesting that cholinergic dysregulation (in particular, nicotinic cholinergic systems) may play a role in the pathophysiology



of ADHD. Independent lines of investigation have documented that ADHD is associated with an increased risk and earlier age at onset of nicotine use and cigarette smoking than in controls without ADHD,<sup>54</sup> that maternal smoking during pregnancy increases the risk for ADHD in the offspring,<sup>55</sup> and that in utero exposure to nicotine in animals confers a heightened risk for an ADHD-like syndrome in the newborn.<sup>56</sup> That nicotinic cholinergic dysregulation could play an important role in the pathophysiology of ADHD is not surprising, considering that animal models show that nicotinic activation enhances dopaminergic and noradrenergic neurotransmission.<sup>57,58</sup>

It is recognized that cholinergic pathways are present in the basal forebrain and that they project diffusely to the cerebral cortex.<sup>59</sup> Thus, pharmacologic enhancement of the cholinergic system could improve a host of cognitive processes, including ADHD and executive deficits. As reviewed by Rezvani and Levin,<sup>58</sup> a substantial literature has demonstrated an improvement in cognitive functioning associated with nicotine administration in subjects without ADHD. Furthermore, improved ADHD has been reported in controlled trials of nicotine<sup>60</sup> and nicotinic analogs.<sup>61,62</sup>

## SUMMARY

In summary, commonalities exist in the mechanism of action of the various agents used in ADHD. Attenuation of central catecholaminergic neurotransmission appears fundamental in the amelioration of ADHD symptoms. Elucidating the various mechanisms of action of ADHD medications will undoubtedly be of major assistance in the future pharmacology of ADHD. Further specific neuroimaging probes will enhance our understanding of the medication-receptor binding characteristics, dynamics, and relationship to outcome. Given our increasing knowledge about pharmacogenomic relationships in ADHD, it is entirely possible that practitioners will choose agents based on a matching of the patient's genotype and the diverse physiologic mechanisms of action of the various medications for ADHD.

*Drug names:* amphetamine (Adderall and others), atomoxetine (Strattera), bupropion (Wellbutrin and others), clonidine (Catapres, Duraclon, and others), desipramine (Norpramin and others), guanfacine (Tenex and others), imipramine (Tofranil and others), methylphenidate (Ritalin, Metadate, and others), modafinil (Provigil), nortriptyline (Pamelor, Aventyl, and others), protriptyline (Vivactil).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, bupropion, clonidine, desipramine, guanfacine, imipramine, modafinil, nortriptyline, and protriptyline are not approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder.

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