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11 Attention Deficit Hyperactivity Disorder and Its Treatment

Attention Deficit Hyperactivity Disorder and Its Treatment Symptoms and Circuits: ADHD as a Disorder of the Prefrontal Cortex 449 ADHD as a Disorder of Inefficient “Tuning” of the Prefrontal Cortex by Dopamine and Norepinephrine 454 Neurodevelopment and ADHD 463 Treatments for ADHD 466 Which Symptoms Should Be Treated First? 466 Stimulant Treatment of ADHD 467 Noradrenergic Treatment of ADHD 480 Future Treatments for ADHD 484 Summary 485 Attention deficit hyperactivity disorder (ADHD) is not just a disorder of “attention,” nor does it have to include “hyperactivity.” Paradigm shifts are altering the landscape for treatment options across the full range of ADHD symptoms, from inattention to impulsivity to hyperactivity, as well as across all the waking hours and across the whole lifespan, from young children through adulthood. This chapter will provide an overview of the psychopharmacology of ADHD, including only short discussions of the symptoms of ADHD. The mechanism of action of treatments classically called stimulants and nonstimulants for ADHD will be emphasized. Information on the full clinical descriptions and formal criteria for how to diagnose and rate ADHD and its symptoms should be obtained by consulting standard reference sources. The discussion here will emphasize the links between various brain circuits and their neurotransmitters with the various symptoms and comorbidities of ADHD and how these are linked to effective psychopharmacological treatments. The goal of this chapter is to acquaint the reader with ideas about the clinical and biological aspects of attention, impulsivity, and hyperactivity. For details of doses, side effects, drug interactions, and other issues relevant to the prescribing of drugs for ADHD in clinical practice, the reader should consult standard drug handbooks (such as Stahl’s Essential Psychopharmacology: the Prescriber’s Guide). SYMPTOMS AND CIRCUITS: ADHD AS A DISORDER OF THE PREFRONTAL CORTEX ADHD is noted for a trio of symptoms: inattention, hyperactivity, and impulsivity (Figure 11-1). It is currently hypothesized that all these symptoms arise from inefficient information processing in various circuits involving the prefrontal cortex (Figures 11-2 through 11-8).

Specifically, the prominent symptom of “inattention” in ADHD can also be described more precisely as “executive dysfunction” and the inability to sustain attention long enough to solve problems. Executive dysfunction is hypothetically linked to inefficient information processing in the dorsolateral prefrontal cortex (DLPFC) (Figures 11-2, 11-3, and 11-7). The DLPFC is activated by a cognitive task known as the n-back test which can be monitored in living patients doing it while in a functional brain scanner (shown in Figure 11-3). Having difficulty in efficiently activating this part of the brain cuts across many psychiatric disorders that share the symptom of executive dysfunction, not just ADHD but also schizophrenia (discussed in Chapter 4), major depression (discussed in Chapter 6), mania (discussed in Chapter 6), anxiety (discussed in Chapter 8), pain (Chapter 9), and disorders of sleep and wakefulness (discussed in Chapter 10). One can see how inefficient information processing in this particular DLPFC circuit, especially when put under a cognitive “load,” can be associated with the same symptom of executive dysfunction and difficulty in sustaining attention and solving problems in many different psychiatric disorders. This is why diagnosis in psychiatry is now progressively moving from describing categorical syndromes that mix together many symptoms to make a diagnosis (as in the DSM and ICD), towards characterizing single symptom dimensions or domains such as executive dysfunction that cut across many psychiatric disorders. The emphasis on symptoms rather than diagnosis is the trend in much of neurobiological research, with the goal of finding better correlates with neuroimaging, biomarkers, and genetics.

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY ADHD: Deconstruct the Syndrome into Diagnostic Symptoms ADHD inattentive symptoms selective attention sustained attention problem solving hyperactive symptoms impulsive symptoms ADHD: Core Symptoms Hypothetically Linked to Malfunctioning Prefrontal Cortex dACC DLPFC selective attention sustained attention problem solving hyperactive symptoms impulsive symptoms cortex prefrontal motor cortex Another dimension of executive dysfunction in ADHD is selective inattention, or not being able to focus, and thus differs from problems with sustaining attention described above. The symptom of problems focusing/ selective inattention is hypothetically linked to inefficient information processing in a different brain area, namely the dorsal anterior cingulate cortex (dACC) (Figures Figure 11-1 Symptoms of ADHD. There are three major categories of symptoms associated with attention deficit hyperactivity disorder (ADHD): inattention, hyperactivity, and impulsivity. Inattention itself can be divided into difficulty with selective attention and difficulty with sustained attention and problem solving. Figure 11-2 Matching ADHD symptoms to circuits. Problems with selective attention are believed to be linked to inefficient information processing in the dorsal anterior cingulate cortex (dACC), while problems with sustained attention are linked to inefficient information processing in the dorsolateral prefrontal cortex (DLPFC). Hyperactivity may be modulated by the prefrontal motor cortex and impulsivity by the orbital frontal cortex. orbitofrontal 11-2, 11-4, and 11-7). The dACC can be activated by tests of selective attention, such as the Stroop test (explained in Figure 11-4). ADHD patients may either fail to activate the dACC when they should be focusing their attention, or they may activate this part of the brain very inefficiently and only with great effort and easy fatiguability.

Assessing Sustained Attention and Problem Solving with the N-Back Test N-back test 2 1 3 4 3 4 3 4 Assessing Selective Attention with the Stroop Task The Stroop Task Blue Red Orange Red Green Green Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment Figure 11-3 Sustained attention and problem solving: the nback test. Sustained attention is hypothetically modulated by a

cortico-striato-thalamo-cortical loop that involves the dorsolateral prefrontal cortex (DLPFC) projecting to the striatal complex. Inefficient activation of the DLPFC can lead to difficulty following through or finishing tasks, disorganization, and trouble sustaining mental effort. Tasks such as the n-back test are used to measure sustained attention and problem-solving abilities. In the 0-back variant of the n-back test, a participant looks at a number on the screen, and presses a button to indicate which number it is. In the 1-back variant, a participant only looks at the first number; when the second number appears the participant is supposed to press a button corresponding to the first number. Higher “n” values are correlated with increased difficulty in the test. inattentive overactivation normal baseline hypoactivation Figure 11-4 Selective attention: the Stroop task. Selective attention is hypothetically modulated by a corticostriato-thalamo-cortical loop arising from the dorsal anterior cingulate cortex (dACC) and projecting to the striatal complex, then the thalamus, and back to the dACC. Inefficient activation of dACC can result in symptoms such as paying little attention to detail, making careless mistakes, not listening, losing things, being distracted, and forgetting things. An example of a test that involves selective attention, and thus should activate the dACC, is the Stroop task. The Stroop task requires the participants to name the color in which a word is written, instead of saying the word itself. For example, if the word “blue” is written in orange, then the correct answer is “orange,” while “blue” is the incorrect choice. inattentive overactivation normal baseline hypoactivation 451

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY impulsivity I know it! overactivation hypoactivation normal baseline Impulsivity Is Modulated by the Orbitofrontal Cortex Figure 11-5 Impulsivity. Impulsivity is associated with a cortico-striatothalamo-cortical loop that involves the orbital frontal cortex (OFC), the striatal complex, and the thalamus. Examples of impulsive symptoms in ADHD include talking excessively, blurting things out, not waiting one’s turn, and interrupting. Motor Hyperactivity Is Modulated by the Prefrontal Cortex hyperactivity overactivation normal baseline hypoactivation Figure 11-6 Hyperactivity. Motor activity, such as hyperactivity and psychomotor agitation or retardation, can be modulated by a corticostriato-thalamo-cortical loop from the prefrontal motor cortex to the putamen (lateral striatum) to the thalamus and back to the prefrontal motor cortex. Common symptoms of hyperactivity in children with ADHD include fidgeting, leaving one’s seat, running/climbing, being constantly on the go, and having trouble playing quietly.

ADHD Core Symptoms: Regional Problems of PFC “Tuning” DLPFC dACC OFC limbic motor cognitive does not finish disorganized avoids sustained effort interrupt blurt out not waiting turn fidget leave seat climb impulsivity problems of selective attention problems of sustained attention & problem solving hyperactivity ADHD Comorbid Symptoms: Additional Problems in the PFC VMPFC limbic steal a car cruelty pick a fight mood instability mania anxiety conduct disorder bipolar/anxiety spectrum Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment Figure 11-7 ADHD core symptoms: regional problems of PFC tuning. The symptoms of ADHD may occur because patients do not activate prefrontal cortical areas appropriately in response to cognitive tasks. Alterations within the orbital frontal cortex (OFC) are hypothesized to lead to problems with impulsivity or hyperactivity. Inadequate tuning of the dorsolateral prefrontal cortex (DLPFC) or the dorsal anterior cingulate cortex (dACC) can respectively lead to sustained or selective attention symptoms. does not listen distracted forgetful careless Figure 11-8 ADHD and comorbid symptoms. Inadequate tuning of the ventromedial prefrontal cortex (VMPFC) may be associated with comorbid symptoms often seen in patients with ADHD, such as symptoms of conduct disorder or oppositional

defiant disorder, as well as mood instability and anxiety. temper tantrums argumentative disobedient aggressive oppositional defiant disorder 453

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Other areas of prefrontal cortex that are hypothetically functioning inefficiently in ADHD are the orbital frontal cortex (OFC), linked to symptoms of impulsivity (Figures 11-2, 11-5, and 11–7), and the supplementary motor area, linked to symptoms of motor hyperactivity (Figures 11-2, 11-6, and 11–7). The OFC is hypothetically linked to a wide variety of symptoms that cut across several psychiatric conditions, including impulsivity in ADHD (Figures 11-2, 11-5, and 11-7), impulsivity and violence in schizophrenia (discussed in Chapter 4), suicidality in depression (discussed in Chapter 6), impulsivity in mania (discussed in Chapter 6), and impulsivity/ compulsivity in substance abuse and related disorders (discussed in Chapter 13). Impulsive symptoms in other psychiatric conditions commonly comorbid with ADHD are also hypothetically related to the OFC such as conduct disorder, oppositional defiant disorder, and bipolar disorder (Figure 11-8). See Chapter 13 for further discussion of impulsivity and compulsivity in a variety of Baseline NE and DA Neuronal Firing Is Tonic PFC NE neuron DA neuron VMAT2 VMAT2 NET NE DA 2B 2C 2A α α α α + + + + + + + + + NE/DA firing tonic firing psychiatric disorders including substance abuse, eating disorders, obsessive–compulsive disorder (OCD), and others. ADHD AS A DISORDER OF INEFFICIENT "TUNING" OF THE PREFRONTAL CORTEX BY DOPAMINE AND NOREPINEPHRINE Hypothetically, ADHD patients do not activate prefrontal cortex areas appropriately in response to cognitive tasks of attention and problem solving (executive functioning) (Figures 11-7 through 11-21). This could be due to the observed neurodevelopmental delays in prefrontal cortical synaptic connections in ADHD (see Figures 11-22 and 11-23), causing inefficient "tuning" of information processing in prefrontal circuits regulated by norepinephrine (NE) and dopamine (DA) Figure 11-9 Baseline norepinephrine and dopamine tonic firing. Modulation of prefrontal cortical function, and therefore regulation of attention and behavior, rely on the optimum release of norepinephrine (NE) and dopamine (DA). Under normal conditions, NE and DA in the prefrontal cortex (PFC) stimulate a few receptors on postsynaptic neurons, allowing for optimal signal transmission and neuronal firing. At modest levels, NE can improve prefrontal cortical functioning by stimulating postsynaptic α2A receptors. Similarly, modest levels of DA will stimulate dopamine 1 and 3 (D1 and D3) receptors and be beneficial to prefrontal cortical functioning. In the case of both the NE and DA systems, moderation is certainly key. D1 D1 D1 D1 + D3 D3 D3 D3 + +

Salience Provokes Phasic DA Neuronal Firing in Reward Centers Nucleus Accumbens DA neuron VMAT2 D1 D2 D2 D1 D1 D2 D2 D2 D2 D2 D1

- ○

D3 D3 D3 D3 D3 D3 D3 D3 D3 D3 D D3 + +

- ○ ○ ○

NE/DA firing tonic firing with burst of phasic firing Figure 11-10 Salience-provoked phasic dopamine firing. While tonic firing, as seen in the prefrontal cortex, is often preferred in neuronal systems, a little bit of phasic firing of dopamine (DA) neurons in the nucleus accumbens can be a good thing. Phasic firing will lead to bursts of DA release and when this happens in a controlled manner it can reinforce learning and reward conditioning, which can provide the motivation to pursue naturally rewarding experiences (e.g., education, career development, etc.). When this system is out of

bounds, however, it can induce uncontrolled DA firing that reinforces the reward of taking drugs of abuse, for example, in which case the reward circuitry can be hijacked, and impulses are followed by the development of uncontrolled compulsions to seek drugs. neurotransmission (Figure 11-9 and Figure 11-10). This is the same arousal network that was discussed in Chapter 10 on sleep and illustrated in Figures 10-1 and 10-44. If the firing of NE neurons innervating the prefrontal cortex is too low in ADHD (Figures 11-11 and 11-12), there would be inadequate “tonic” NE stimulation setting the baseline “tone” of noradrenergic neurotransmission Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment too low. Low NE tone hypothetically contributes to the cognitive dysfunction in ADHD (Figure 1111) and preferentially stimulates the most sensitive noradrenergic receptors on postsynaptic neurons (Figure 11-12). Increasing NE levels modestly would hypothetically improve prefrontal cortical function by stimulating the more sensitive postsynaptic α2A receptors (Figure 11-12) but increasing NE too high – as may occur in stressful situations or in various comorbid conditions such as anxiety, substance abuse, and mania – could lead to impaired working memory when the less sensitive α1 and β1 receptors are also recruited (Figures 11-13 to 11-15). Thus, NE neurotransmission must occur within a “sweet spot” of neither too high nor too low (Figure 11-15) in order to optimize cognitive functioning. Similarly, if the firing of DA neurons innervating the prefrontal cortex is also too low in ADHD, there would hypothetically be inadequate “tonic” DA stimulation, setting the baseline “tone” of the DA synapse too low at rest (Figures 11-11 and 11-12). Low release of DA preferentially stimulates the most sensitive DA receptors on postsynaptic neurons (i.e., D3 receptors; Figure 11-9; see also Chapter 4 and Figure 4-9) but inadequately stimulates the less sensitive D1 receptors (Figures 11-11, 11-12, 11-15, and 11-16), and this would cause inadequate downstream neuronal signaling and cognitive dysfunction. Increasing DA levels modestly would hypothetically improve prefrontal cortical function in part by first boosting tonic signaling at D3 receptors, then at moderately sensitive D2 receptors, and finally at the least sensitive D1 receptors (Figures 11-9, 11-11 through 11-13, 11-15, and 11–16; see also Chapter 4 and Figure 4-9). Dopamine neurons also exhibit bursts of firing called phasic DA stimulation (Figure 11-10), with a flurry of dopamine release that recruits all three DA receptor subtypes. Phasic DA release is thought to reinforce learning and reward conditioning, providing the motivation to pursue naturally rewarding experiences. The DA system is adaptively programmed to fire in a phasic manner when there are pertinent and notable sensory inputs such as those associated with education, recognition, career development, enriching social and family connections, etc. Enhancing phasic DA signaling modestly so that cognitive tasks can be performed efficiently is hypothetically the therapeutic goal in treatment of ADHD. However, when the phasic DA system is overly activated by stress or comorbid 455

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY receptor stimulation is what is thought to be beneficial to set the optimal tone and to optimize prefrontal cortical functioning (Figures 11-15 and 11-16). Postsynaptic D1 receptors predominate in the prefrontal cortex and the best functional outcome is when they are “tuned” and neither understimulated nor overstimulated (Figures 11-15 and 11-16). conditions such as anxiety, substance abuse, or mania, it worsens cognitive functioning with too much arousal (Figures 11-13 through 11-16). The phasic DA system can even be hijacked by drugs, and induce uncontrolled DA firing, reinforcing the reward of drugs, leading to compulsive drug abuse (discussed extensively in Chapter 13). Therefore, moderate, but not high or low, levels of D1 Figure 11-11 Cognitive function in ADHD: is it deficient? Arousal exists as if on a dimmer switch, with many phases along the spectrum. Where on the spectrum one lies is influenced by several key wake-promoting neurotransmitters, including histamine (HA), dopamine (DA),

norepinephrine (NE), serotonin (5HT), and acetylcholine (ACh). When neurotransmission is balanced, one is awake, alert, and able to function well. Alterations in the functioning of these key neurotransmitters, whether too much or too little, can cause cognitive dysfunction. Cognitive dysfunction in ADHD may be a result of low tonic noradrenergic and dopaminergic firing. $ asleep inattentive panic/fear hypervigilant/ insomnia awake alert creative problem solving excessive daytime sleepiness/ drowsiness/ sedation cognitive dysfunction (understimulation) cognitive dysfunction (overstimulation) 5HT NE DA ACh HA deficient arousal excessive arousal hallucinations/ psychosis Cognitive Function in ADHD: Is It Deficient? low tonic firing NE/DA firing inattentive impulsive I know it! hyperactive overactivation hypoactivation normal baseline

ADHD and Deficient Arousal: Weak NE and DA Signals PFC NE neuron DA neuron VMAT2 VMAT2 NET NE DA 2B 2C 2A α α α α + In the prefrontal cortex, α2A and D1 receptors are often located on the spines of cortical pyramidal neurons, and can thus gate incoming signals (Figures 11-17 through 11-21). Alpha-2A receptors are linked to the molecule cyclic adenosine monophosphate (cAMP) via the inhibitory G protein (Gi) (Figure 11-17). D1 receptors, on the other hand, are linked to the cAMP signaling system via the stimulatory G protein (Gs) (Figure 11-17). In either case, the cAMP molecule links the receptors to the hyperpolarization-activated cyclic nucleotide-gated (HCN) cation channels. An open channel will lead to a low membrane resistance, thus shunting inputs out of the spine. In the presence of an open channel, the signal leaks out and is therefore lost. However, when these channels are closed, the incoming signal survives and can be directed down the neuron to strengthen the network connectivity of similar neurons and lead to the appropriate signal and response. When NE, or a noradrenergic agonist, binds to an α2A receptor, the activated Gi-linked system inhibits cAMP, thereby closing the HCN channel (Figure 11-18). Closure of the channel allows the signal to go through the spine Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment Figure 11-12 ADHD and deficient arousal. Besides being a key player in the arousal pathways, the prefrontal cortex (PFC) is also the main brain area where imbalances in norepinephrine (NE) and dopamine (DA) systems hypothetically occur in ADHD. Deficient signaling in prefrontal cortical NE and DA pathways is reflected by reduced stimulation of postsynaptic receptors. Specifically, D1 receptors, which are relevant to cognitive functioning, are not very sensitive to dopamine; thus, they are not stimulated when DA levels are low. Increasing levels of NE and DA would hypothetically improve prefrontal cortical functioning through increased stimulation of postsynaptic α2A receptors and increased stimulation of D1 receptors. D1 D1 D1 D1 + and down the neuron, thereby strengthening network connectivity with similar neurons (Figure 11-18). So, in general, in the prefrontal cortex, stimulation of α2A receptors strengthens an incoming signal. By contrast, stimulation of D1 receptors leads to weakening of the signal (Figure 11-19). That is, when DA, or a DA agonist, binds to a D1 receptor, the activated Gs-linked system will lead to increased stimulation – or opening – of HCN channels. The opening of the HCN channels, especially if excessive, will lead to leakage of the signal, thereby shunting any input out of the spine. So, excessive stimulation of D1 receptors will, in contrast to stimulation of α2A receptors, result in the dissipation and/or weakening of a signal. The mechanism of action of α2A (Figure 11-18) and D1 receptors (Figure 11-19) explains in general why moderate stimulation of both types of receptors (Figure 11-17) is preferred in order to strengthen the signal-to-noise ratio in prefrontal cortical neurons (see Figure 11-20). What happens following concurrent stimulation of α2A and D1 receptors by NE and DA, respectively (Figure 11-20)? While the exact localization and density of α2A and D1 receptors within various cortical areas are still 457

 in adequate guided attention (Figures 11-15, 11-16), focus on a specific task, and adequate control of emotions and impulses. What happens, however, when there is low release of both DA and NE and thus low stimulation of both D1 and α2A receptors on the spines of these pyramidal neurons (Figure 11-21)? Deficient DA and NE input will theoretically lead to increased noise and decreased under intense investigation, it is possible to imagine the same pyramidal neuron receiving NE input from the locus coeruleus (LC) on one spine and DA input from the ventral tegmental area (VTA) on another spine. If the systems are properly "tuned," D1 receptor stimulation can reduce the noise and α2A receptor stimulation can increase the signal to result in proper prefrontal cortex functioning (Figure 11-20). Theoretically, this will result Figure 11-13 Cognitive function in ADHD: is it excessive? Arousal exists as if on a dimmer switch, with many phases along the spectrum. Where on the spectrum one lies is influenced by several key wake-promoting neurotransmitters, including histamine (HA), dopamine (DA), norepinephrine (NE), serotonin (5HT), and acetylcholine (ACh). When neurotransmission is balanced, one is awake, alert, and able to function well. Alterations in the functioning of these key neurotransmitters, whether too much or too little, can cause cognitive dysfunction. Increasing norepinephrine or dopamine too high could lead to excessive stimulation of postsynaptic receptors and cause cognitive dysfunction. bipolar substance abuse anxiety $ 5HT NE DA ACh HA deficient arousal excessive arousal asleep inattentive panic/fear hallucinations/ psychosis hypervigilant/ insomnia awake alert creative problem solving excessive daytime sleepiness/ drowsiness/ sedation cognitive dysfunction (understimulation) cognitive dysfunction (overstimulation) overactivation hypoactivation normal baseline Cognitive Function in ADHD: Is It Excessive? $

ADHD and Excessive Arousal: Impact of Stress and Comorbidities PFC NE neuron DA neuron stress 2B 2C 2A α α α α D1 D1 D1 D1 ++ ++ ++ ++ + + ++ ++ + + + + + + + + ++ ++ ++ ++ ++ ++ + + + + + ++ ++ ++ ++ ++ ++ + + + + + inattention/ problems concentrating from excessive arousal alcohol abuse/ impulsivity anxiety from excessive arousal Tuning Cortical Pyramidal Neurons in ADHD pyramidal cell function α optimal D1, 2A activity α α α D1, 2A too low Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment Figure 11-14 ADHD and excessive arousal. When norepinephrine (NE) and dopamine (DA) neurotransmission in the prefrontal cortex (PFC) are optimally tuned, modest stimulation of postsynaptic α2A receptors and D1 receptors allows for efficient cognitive functioning. If NE or DA neurotransmission is excessive, as in situations of stress or comorbid conditions such as anxiety or substance abuse, this can lead to overstimulation of postsynaptic receptors and consequently to cognitive dysfunction as well as other symptoms. Specifically, excessive noradrenergic neurotransmission can lead to impaired working memory due to stimulation of α1 (and β1) receptors. Excessive dopaminergic neurotransmission can lead to overstimulation of D1 receptors in the prefrontal cortex. Figure 11-15 ADHD and maladaptive signal-to-noise ratios. In order for the prefrontal cortex to work properly, moderate stimulation of α2A receptors by norepinephrine (NE) and of D1 receptors by dopamine (DA) is required. In theory, the role of NE is to increase the incoming signal by allowing for increased connectivity of the prefrontal networks, while the role of DA is to decrease the noise by preventing inappropriate connections from taking place. At the top of the inverted U-shaped curve depicted here, stimulation of both α2A and D1 receptors is moderate and pyramidal cell function is optimal. If stimulation at α2A and D1 receptors is too low (left side), all incoming signals are the same, making it difficult for a person to focus on one single task (unguided attention). If stimulation is too high (right side), incoming signals get jumbled as additional receptors are recruited, resulting in the misdirection of attention. D1, 2A too high; 1 stimulation recruited

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 11-16 Functional output of cortical dopamine. In order for the prefrontal cortex (PFC) to work properly and for cognitive performance to be optimized, moderate stimulation of α2A receptors by norepinephrine (NE) and D1 receptors by dopamine (DA) is required. If stimulation at α2A and D1 receptors is either too low or too high, cognitive dysfunction can occur. cognitive symptoms 2A D1, α 2A D1, α activity optimal Neurotransmitter Levels (PFC) Functional Output of Cortical Dopamine Cognitive Performance dopamine receptor activity too high dopamine receptor activity too low Figure 11-17 Signal distribution in a dendritic spine. The location of α2A and D1 receptors on dendritic spines of cortical pyramidal neurons in the prefrontal cortex allows them to gate incoming signals. Both α2A and D1 receptors are linked to the molecule cyclic adenosine monophosphate (cAMP). The effects on cAMP from norepinephrine (NE) and dopamine (DA) binding at their respective receptors are opposite (inhibitory in the case of NE and excitatory in the case of DA). In either case, the cAMP molecule links the receptors to the hyperpolarization-activated cyclic nucleotide-gated (HCN) cation channels. When HCN channels are open, incoming signals leak out before they can be passed along. However, when these channels are closed, the incoming signal survives and can be directed down the neuron. NE incoming information signal lost/ leaks out surviving signal strength signal lost/ leaks out cAMP cAMP DA Signal Distribution in a Dendritic Spine 2A α D1

NE Actions at Alpha -2A Receptors Strengthen Signal NE cAMP 2A α cAMP strengthened signal DA Actions at D1 Receptors Weaken Signal cAMP D1 cAMP DA weakened or lost signal Figure 11-18 Norepinephrine actions at α2A receptors strengthen the incoming signal. Alpha-2A receptors are linked to cyclic adenosine monophosphate (cAMP) via an inhibitor G protein (Gi). When NE occupies these α2A receptors, the activated Gi-linked system inhibits cAMP and the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel is closed, preventing loss of the incoming signal. incoming information Figure 11-19 Dopamine actions at D1 receptors weaken the incoming signal. D1 receptors are linked to cyclic adenosine monophosphate (cAMP) via a stimulatory G protein (Gs). When dopamine (DA) occupies these D1 receptors, the activated Gs-linked system activates cAMP leading to opening of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. The opening of HCN channels, especially if excessive, will lead to loss of the incoming signal before it can be passed along. incoming information 461

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 11-20 Dopamine and norepinephrine “tune” the prefrontal cortex (PFC). The same pyramidal neuron may receive norepinephrine (NE) input from the locus coeruleus (LC) on one spine and dopamine (DA) input from the ventral tegmental area (VTA) on another spine. When properly “tuned,” D1 receptor stimulation will reduce the noise while α2A receptor stimulation will increase the signal, resulting in appropriate prefrontal cortical functioning, guided attention, focus on a specific task, and control of emotions and impulses. LC normal DA release noise noise reduced signal increased signal normal NE release VTA How DA and NE Hypothetically “Tune” the PFC: Signal Increased and Noise Reduced Figure 11-21 Dopamine and norepinephrine improperly “tune” the prefrontal cortex (PFC) in ADHD. The same pyramidal neuron may receive norepinephrine (NE) input from the locus coeruleus (LC) on one spine and dopamine (DA) input from the ventral tegmental area (VTA) on another spine. Deficient DA input will theoretically lead to increased noise, while deficient NE input will cause a decrease in the incoming signal. Hypothetically, this improper tuning of the PFC by DA and NE can lead to hyperactivity, or inattention, or both. noise increased signal reduced How DA and NE Hypothetically “Tune” the PFC: Low NE and Low DA: ADHD with Signals Reduced and Noise Increased LC low DA release noise

signal low NE release VTA

signal, respectively, thus preventing a coherent signal from being sent (Figure 11-21). Hypothetically, this could cause hyperactivity, inattention, impulsivity, or some combination of symptoms, depending upon the localization of the mis-tuned pyramidal neuron in the prefrontal cortex (see Figures 11-3 through 11-8). Furthermore, if one neurotransmitter is low while the other is high, then a person could be exhibiting a whole different set of symptoms. By knowing both the levels of DA and NE neurotransmission and the specific area of the possible disturbances, it may one day be possible to predict the degree and type of symptoms from which a patient is ailing. With this in mind, Figures 11-7 and 11-8 show how pyramidal neurons in different brain areas may be responsible for the different symptom presentations in ADHD. NEURODEVELOPMENT AND ADHD ADHD is traditionally considered a childhood disorder, but the concept of ADHD has evolved to be considered childhood in onset but often persisting into adulthood. In fact, most psychiatric disorders have onset in childhood and young adult years and then persist into adulthood (Figures 11-22 and 11-23). The reason for this may be that childhood and young-adult development is when the brain is undergoing critical maturation (Figure 11-22A and 11-23). Brain development is directed by both genetic and environmental influences (discussed for psychotic disorders in Chapter 4 and illustrated in Figures 4-61 and 4-62). ADHD has one of the strongest genetic components in psychiatry at about 75%. Multiple genes are implicated in ADHD and the genetic causation is complex and multifactorial, as it is in any mental disorder. A unifying formulation of ADHD is that it is caused by delayed maturation of prefrontal cortex circuitry that manifests in ADHD symptoms at least by age 12. Synapses rapidly increase in the prefrontal cortex by age 6, and then up to half of them are rapidly eliminated by adolescence (Figure 11-22A; see also Chapter 4 and Figures 4-63 and 4-64). The timing of onset of ADHD suggests that the formation of synapses and, perhaps more importantly, the selection of synapses for removal in the prefrontal cortex during childhood may contribute to the onset and lifelong pathophysiology of this condition (Figures 11-22 and 11-23). Those who Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment are able to compensate for these prefrontal cortical abnormalities by new synapse formation after age 12 and into early adulthood may be the ones who “grow out of their ADHD” and why the prevalence of ADHD in adults is only half that in children and adolescents. What causes these problems in the circuits of the prefrontal cortex in ADHD? Currently, leading hypotheses propose that neurodevelopmental abnormalities occur in the circuits of the prefrontal cortex in ADHD (Figures 11-2 through 11-8). Many of the ideas about the neurodevelopmental basis of schizophrenia, such as abnormal synapse formation and abnormal synaptic neurotransmission, serve as a conceptual framework and neurobiological model for ADHD as well, and are discussed in Chapter 4. The impact of neurodevelopment on the specific symptom patterns of ADHD is shown in Figure 11-24. Inattentive symptoms can exist but are not easily identified in preschool children with ADHD, perhaps because they do not have a sufficiently mature prefrontal cortex to manifest this symptom in a manner that is abnormal compared to normal development. Preschool ADHD and its treatment are a current controversial concept in the field because most studies of stimulants involve children over the age of 6. Once inattention becomes a prominent symptom of ADHD, it remains so over the life cycle (Figure 11-24). However, impulsivity and hyperactivity decline notably by adolescence and early adulthood, while recognized comorbidities skyrocket in frequency as ADHD patients enter adulthood (Figure 11-24). The diagnostic criteria most recently changed from requiring onset prior to age 7 in the past diagnostic schemes of DSM-IV, now to onset prior to age 12 in DSM5. There is even debate as to whether or not there is such a

thing as adult-onset ADHD (or at least recognized first as an adult with unclear onset). The prevalence of ADHD in adults may be only about half of that in children, but it is not recognized nearly as often as it is in children, possibly because it is much harder to diagnose and its symptoms are very often not treated. Whereas half of all children or adolescents with ADHD are thought to be diagnosed and treated, less than one in five adults with ADHD is thought to be diagnosed and treated. The reasons for this are multiple, starting with the diagnostic requirement that ADHD symptoms must begin by age 12. Adults often have difficulty making accurate retrospective diagnoses, especially if the condition was not identified 463

Synaptogenesis in Prefrontal Cortex and the Development of Executive Functions Most Psychiatric Disorders Have Onset in Child and Young-Adult Years During Cortical Development newborn A B years age at onset (years) number of synapses in PFC percent 2 6 10 14 7-9 0-3 13-15 25-27 working memory emerges executive functioning emerges age at which inattentive symptoms of ADHD become noticeable rapid expansion of executive functions attending to one task while ignoring irrelevant stimuli; cognitive flexibility and inhibition; verbal memory performance preschool: little ability to sustain attention on task; easily distracted by irrelevant stimuli planning skills emerge; ability to sustain attention on one task but not perseverate; recognition memory; formation of abstract concepts Age 6 Birth Age 14-60 5 15 40 80 Figure 11-22 Cortical development and ADHD. Synaptogenesis in the prefrontal cortex (PFC) might be responsible for altered connections that could prime the brain for ADHD. Specifically, executive function develops throughout adolescence. (A) At 1 year of age, working memory emerges. Around 3–4 years of age, children do not yet have the capability to sustain attention for long periods of time, and can be easily distracted. By age 6–7, this changes; attention can be sustained and planning can take place. This age is also characterized by “synaptic pruning,” a process during which overproduced or “weak” synapses are “weeded out,” thus allowing for the child’s cognitive intelligence to mature. Errors in this process could hypothetically affect the further development of executive function and be one of the causes of ADHD. This timeline also represents when symptoms of ADHD often become noticeable, which is around the age of 6. (B) Most psychiatric disorders have onset in childhood and young-adult years and then persist into adulthood, coinciding with critical cortical development.

Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment patients have ADHD? Or is their executive dysfunction a symptom of a comorbid disorder such as depression, anxiety, or sleep disorder? The point is to screen for cognitive symptoms and to treat them, whether part of an ADHD disorder or a comorbidity. and treated as a child. Furthermore, many experts now question whether it is appropriate to exclude from the diagnosis of ADHD those adults whose ADHD symptoms started after age 12, so-called late-onset ADHD. Some cases may even have onset up to the age of 45. Do these Figure 11-23 Developmental course of brain maturation and onset of psychiatric disorders. The developmental course of brain development is such that the sensorimotor cortex and limbic brain regions develop first, and the prefrontal cortex develops later. In ADHD, this same pattern is observed; however, cortical development is delayed. This may account for the childhood onset of ADHD and why, although ADHD may continue into adulthood, its onset does not occur in adulthood. In contrast, other disorders can also begin in childhood but are typically diagnosed later than ADHD, with onset continuing into adulthood. Developmental Course of Brain Maturation Median Age at Onset of Psychiatric Disorders Across Development age (years) 5 15 25 Sensorimotor Cortex Amygdala Striatum Hippocampus Prefrontal Cortex age (years)

relative incidence ADHD/ Conduct Anxiety Disorders Substance Abuse Schizophrenia Mood Disorders 10 20 465

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Impact of Development on ADHD inattention impulsivity comorbidity recognized hyperactivity subthreshold adolescence preschool school age

- academic problems
- difficulty with social interactions
- self-esteem issues
- legal issues, smoking and injury
- behavioral disturbances
- behavioral disturbances
- academic problems
- difficulty with social interactions
- self-esteem issues TREATMENTS FOR ADHD Which Symptoms Should Be Treated First? It can be helpful in managing ADHD to prioritize which symptoms to target first with psychopharmacological treatments, even at the expense of delaying treatment for a while for some conditions, or even making some of these comorbid conditions transiently worse if other symptoms are targeted for improvement first (Figure 11-25). Although there are no definitive studies on this approach, clinical experience from many experts suggests that, in complex cases, it can be very difficult to make any therapeutic progress if the patient continues to abuse alcohol or stimulants; thus, substance abuse problems must often be managed top line (Figure 11-25). Treating ADHD may also have to await improvement from mood and anxiety disorder treatments, with ADHD cognitive symptoms seen as more of a fine-tune adjustment to a patient's overall symptom portfolio (Figure 11-25). There are problems, however, with this approach of setting priorities of which symptoms and disorders to treat first. For example, many children are treated for their ADHD first, and without adequately evaluating possible comorbidities until patients fail to respond robustly to stimulant treatment. In adults, it can be so Figure 11-24 Impact of development on ADHD. Consistent with our understanding of neurodevelopment, the evolution of symptoms in ADHD shows that inattention is generally not identified in preschool but becomes prevalent as the patient ages and continues into adulthood. Hyperactivity and impulsivity are key symptoms in childhood but are less likely to manifest overtly in adulthood, although they may simply be expressed differently. The rates of comorbidities increase over time; this could be due to the fact that the comorbidities were overlooked in children with ADHD or that they truly develop later, consistent with data showing later onset of other psychiatric disorders compared to ADHD. college age adulthood
- academic failure
- occupational difficulties
- self-esteem issues
- substance abuse
- injury/accidents
- occupational failure
- self-esteem issues
- relationship problems

- injury/accidents
- substance abuse difficult to treat substance abuse, mood disorders, and anxiety disorders that the focus of therapeutic attention never gets to ADHD, and certainly not to nicotine dependence. That is, ADHD can be considered a mere afterthought in adults to be addressed if cognitive symptoms do not remit once the primary focus of therapeutic intervention, namely the mood or anxiety disorder, is treated. It is interesting that ADHD is not often the focus of treatment in adults unless it presents with no comorbid conditions. Since lack of comorbidity in adults with ADHD is rare, this may explain why the majority of adults with ADHD are not treated. The modern, sophisticated psychopharmacologist keeps a high index of suspicion for the presence of ADHD in mood, anxiety, and substance abuse disorders especially in adults, always aiming for complete symptomatic remission in patients under treatment. In practice, this means exploring the use of ADHD treatments as augmenting agents to first-line treatments of mood, anxiety, and substance abuse disorders, rather than the other way around. It also means that longterm management of ADHD is eventually to address the treatment of nicotine dependence in ADHD once cognitive symptoms are under control (Figure 11-25). Adults and adolescents with ADHD smoke as frequently

alcohol/stimulant/ substance abuse mood disorders order of treatment anxiety disorders ADHD treatment in adults often ends here as adults and adolescents with schizophrenia, about twice the rate of the normal population in the US. This may be due to the fact that nicotine subjectively improves ADHD symptoms, especially in patients who are not treated for their ADHD. Nicotine enhances dopamine release and enhances arousal, so it is not surprising that it may be subjectively effective for ADHD symptoms. Nicotine dependence and psychopharmacological treatments for smoking cessation are discussed in more detail in Chapter 13 on impulsivity, compulsivity, and addiction. Stimulant Treatment of ADHD General Principles As discussed above and as illustrated in Figures 11-11 and 11-12, when both DA and NE are too low, the strength of signal output in the prefrontal cortex is also too low, thus leading to reduced signal and increased noise (Figure 11-26A; see also Figures 11-15, 11-16, and 11-21). Behaviorally, this could translate into a person not being able to sit in his/her seat and focus, and to fidget and shift attention, respectively (Figure 11-26A). In order to treat these symptoms, it is necessary to increase signal strength output by dialing up the release of both DA and NE until they reach the optimal levels (Figure 11-26B). This can Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment Figure 11-25 ADHD and comorbidities: what should be treated first? In a patient with ADHD and comorbid disorders, it is imperative to treat all disorders appropriately, and in terms of highest degree of impairment. This might mean that in one patient it is necessary to first stabilize the alcohol abuse, while in another patient the symptoms of ADHD might be more impairing than the underlying anxiety disorder. Additionally, some medications used to treat these disorders could exacerbate the comorbid ailment. Thus, care needs to be taken when choosing the appropriate treatment. An individualized treatment plan should be established for each patient based on his/her symptomatic portfolio. nicotine dependence treatment in children/adolescents often begins here be done both by norepinephrine and dopamine reuptake blocking stimulants and by some noradrenergic agents as discussed below. Strengthening prefrontal cortical output is hypothesized to be beneficial in restoring a patient’s ability to tease out important signals from unimportant ones, and to manage to sit still and focus. What if NE and DA signals are excessive? Excessive as well as deficient activation of NE and DA in the prefrontal cortex can lead to ADHD, as discussed

above, namely by increasing the noise and decreasing the signal (see Figures 11-13 through 11-16). The theory is that at first, and in some patients, the added stress of suffering from ADHD plus other stressors from the environment can even further dial up the noise and reduce the signal, resulting at first in high NE and DA release, causing reduced signals and inefficient information processing (Figure 11-27A). As stress becomes chronic, however, NE and DA levels eventually plummet due to depletion over time, but with no relief in terms of poor signal output (Figure 11-27B). Ultimately the appropriate treatment is to increase NE and DA concentrations to allow for normalization of behavior (Figure 11-27C, noise is reduced and signal is increased). 467

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Importance of NE and DA Levels in PFC in ADHD ADHD: Hypothetically Low Signals and/or High Noise in PFC PFC strength of output PFC strength of output PFC noise signal NE concentration fidget / shift attention sit in seat / focus A Treatment: Increase NE, Increase DA PFC strength of output PFC strength of output PFC noise signal NE concentration fidget / shift attention sit in seat / focus B Experienced clinicians are well aware that such patients with too much DA and NE (represented in Figure 11-27A), too little DA and NE (represented in Figure 11-27B), or a combination of these in different pathways, can be very difficult to treat. For example, in children, the combination of tics generally representing hypothetically excessive DA activation in the motor striatum, and requiring DA blockade for treatment, can be very difficult to manage simultaneously in patients with ADHD who have hypothetically deficient DA activation in the cortex, requiring DA-enhancing stimulants. Stimulants may help the ADHD symptoms but worsen the tics. Children and adolescents who have conduct disorder, oppositional disorders, intermittent explosive disorder, disruptive behavioral disorder, psychotic disorders and/or bipolar mania, or mixed conditions (theoretically associated with excessive DA activation in some prefrontal circuits) (Figure 11-8), who are unlucky enough to have comorbid ADHD (theoretically associated with deficient DA activation in different prefrontal circuits) (Figure 11-7), are among the most challenging patients for clinicians. Figure 11-26 The importance of norepinephrine and dopamine levels in the prefrontal cortex in ADHD. (A) When both norepinephrine (NE) and dopamine (DA) are too low (on the left side of the inverted U-shaped curve), the strength of output in the prefrontal cortex (PFC) is too low, leading to reduced signal and increased noise. The inability to sit still and focus, together with fidgeting and shifting attention, are often clinical manifestations of this imbalanced signal-to-noise ratio. (B) In order to treat these symptoms, it is necessary to increase strength output by dialing up the concentrations of both NE and DA until they reach the optimal dose (top of the inverted U-shaped curve). DA concentration NE low - signal reduced DA low - noise increased DA concentration NE optimized - signal increased DA optimized - noise reduced Thus, conditions associated with hypothetically excessive DA activation suggest treatment with dopamine blocking agents (see Chapter 5), yet comorbid ADHD suggests treatment with a stimulant. Can dopamine blockers and stimulants be combined? In fact, in heroic cases, stimulants can be combined with serotonin– dopamine antagonists. The rationale for this combination exploits the fact that serotonin–dopamine blockers hypothetically release DA in the prefrontal cortex, to stimulate postsynaptic D1 receptors there (see Figure 5-17C), while simultaneously blocking D2 receptors in limbic areas, to reduce DA activity at D2 receptors there. Such an approach is controversial and best left to experts for difficult patients who fail to improve adequately on monotherapies. This mechanism of action of dopamine– serotonin blockers and their actions in different areas of the brain are discussed in detail in Chapter 5. For patients with ADHD and anxiety, it can be difficult or even self-defeating to try to improve the ADHD with stimulant treatment, only to cause the anxiety to worsen. For

patients with ADHD and substance abuse, it makes little sense to give stimulants to drug abusers in

Effects of Chronic Stress in ADHD PFC strength of output PFC noise signal NE concentration fidget / shift attention sit in seat / focus A PFC strength of output PFC noise signal NE concentration fidget / shift attention sit in seat / focus B PFC strength of output PFC noise signal NE concentration fidget / shift attention sit in seat / focus C order to treat their ADHD. In these cases, augmenting antidepressant or anxiolytic therapies with a tonic activator of DA and/or NE systems, such as a longlasting norepinephrine transport (NET) inhibitor or an α2A-adrenergic agonist, rather than a stimulant, can be an effective long-term approach for comorbid anxiety, depression, or substance abuse with ADHD. Some studies of NET inhibitors report improvement in both ADHD and anxiety symptoms, and other studies report improvement in both ADHD and heavy drinking. Methylphenidate The mechanism of action of the so-called stimulants – perhaps better designated as norepinephrine and dopamine reuptake blockers – is shown in Figures 11-28 through Figure 11-37. Oral administration of clinically approved doses of the stimulant methylphenidate blocks Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment Figure 11-27 Chronic stress in ADHD. Excessive activation of norepinephrine (NE) and dopamine (DA) in the prefrontal cortex (PFC) can lead to ADHD by increasing the noise and decreasing the signal. (A) At first, the added stress of suffering from the disorder can further dial up the noise and reduce the signal (high NE and DA concentration leading to decreased output). (B) As chronic stress sets in, NE and DA levels plummet (low NE and DA concentration also leading to decreased output), but with no relief in terms of signal output. (C) Treatments that increase NE and DA concentrations may reduce symptoms by increasing strength output (noise is reduced and signal is increased). ADHD and Stress: Hypothetically Low Signals and/or High Noise in PFC At first, high NE and DA PFC strength of output DA concentration NE high - signal reduced DA high - noise increased Chronic Stress Eventually, NE and DA depletion PFC strength of output DA concentration NE low - signal reduced DA low - noise increased Treatment: Increase NE, Increase DA PFC strength of output DA concentration NE optimized - signal increased DA optimized - noise reduced the transporters both for NE and DA (NETs and DATs, respectively) (Figures 11-28 and 11-29A–C). Normally, DA is released (arrow 1 in Figure 11-29A), and then taken back up into the dopaminergic neuron by DATs (arrows 2 in Figure 11-29A), and finally stored in the synaptic vesicle by VMATs (arrows 3 in Figure 11-29A). Methylphenidate blocks DATs and NETs allosterically, stopping the reuptake of DA via DATs (Figure 11-29B) and NE via NETs (Figure 11-29C), with no actions on VMAT2 (Figures 11-29B and 11-29C). Methylphenidate blocks NETs and DATs in much the same way as reuptake blockers used to treat depression (see discussion in Chapter 7 and Figure 7-36), namely by binding to NETs and DATs at sites distinct from where monoamines bind NETs and DATs, i.e., allosterically. Thus, methylphenidate stops the reuptake pumps so that no methylphenidate is 469

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Methylphenidate is also available as the single enantiomer D-methylphenidate, in both immediate-release and controlled-release preparations. A listing of the wide range of D,L-methylphenidate preparations is shown in Table 111, and those for D-methylphenidate shown in Table 11-2. transported into the presynaptic neuron (Figure 11-29B and 11-29C). Methylphenidate has a D- and an L-isomer (Figure 11-28), with the D-isomer being much more potent than the L-isomer on both NET and DAT binding. Table 11-1 D,L-Methylphenidate formulations Formulation Brand names Duration Dosing Approval Immediate-release tablet Ritalin Early peak, 3–4-hr duration Second dose at lunch Ages 6 to 12 and adults

Immediate-release oral solution Methylin Early peak, 3–4-hr duration Second dose at lunch Ages 6 to 12 Extended-release tablet Ritalin SR Methylin ER Metadate ER Early peak, 3–8-hr duration Lunch dosing may be needed Ages 6 and older Extended-release tablet Concerta Small early peak, 12-hr duration Once daily in the morning Ages 6 and older Extended-release chewable tablet QuilliChew ER Peak at 5 hr, 8-hr duration Once daily in the morning Ages 6 and older Extended-release capsule Metadate CD Strong early peak, 8-hr duration Once daily in the morning Ages 6 to 17 Extended-release capsule Ritalin LA Two strong peaks (early and at 4 hrs), 6–8-hr duration Once daily in the morning Age 6 to 12 Extended-release capsule Aptensio XR Up to 12-hr duration Once daily in the morning Ages 6 and older Extended-release oral suspension Quillivant XR Peak at 5 hr, 12-hr duration Once daily in the morning Ages 6 and older Extended-release transdermal patch Daytrana One peak at 7–10 hrs, 12hr duration Once daily in the morning Ages 6 to 17 Orally disintegrating tablet Cotempla XR-ODT 12-hr duration Once daily in the morning Ages 6 to 17 Extended-release capsule Jornay PM Initial absorption delayed by 10 hrs, single peak at 14 hrs Once daily in the evening Ages 6 and older Extended-release capsule Adhansia XR Two peaks (at 1.5 and 12 hrs) Once daily in the morning Ages 6 and older Table 11-2 D-Methylphenidate formulations Formulation Brand Names Duration Dosing Approval Immediate-release tablet Focalin Early peak, 4–6-hr duration Second dose at lunch Ages 6 to 17 Extended-release capsule Focalin XR Two peaks (after 1.5 and 6.5 hrs), 8–10-hr duration Once daily in the morning Ages 6 to 17 and adults

D,L-Methylphenidate NET NET DAT DAT D-methylphenidate L-methylphenidate Regulation of the Transport and Availability of Synaptic DA VMAT 2 2 dopamine (DA) 1 = release of DA 2 = DAT transport of DA 3 = VMAT transport of DA A Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment Figure 11-28 D,L-methylphenidate. Methylphenidate consists of two enantiomers, D and L; both racemic D,L-methylphenidate and D-methylphenidate are available as therapeutic options. D,L-methylphenidate and D-methylphenidate both block the norepinephrine transporter (NET) and the dopamine transporter (DAT). D-methylphenidate has greater potency for both transporters than does the L enantiomer. Figure 11-29A Regulation of transport and availability of synaptic dopamine. The regulation of synaptic dopamine (DA) is dependent upon proper functioning of two transporters, namely the dopamine transporter (DAT) and the vesicular monoamine transporter (VMAT). After DA is released (1) it can act at postsynaptic receptors or it can be transported back into the terminal via DATs (2). Once inside the terminal, DA is “encapsulated” into vesicles via VMAT (3). These DAfilled vesicles can then merge with the membrane and lead to more DA release. This finely tuned machinery ensures that DA levels never reach toxic levels in the synapse or in the DA terminal. By “engulfing” DA into vesicles it is possible for the DA neuron to ensure the viability of DA. 471

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Mechanism of Action of Methylphenidate DA neuron methylphenidate B Figure 11-29B Mechanism of action of methylphenidate at dopamine neurons. Methylphenidate blocks the reuptake of dopamine (DA) into the terminal by binding at an allosteric site (i.e., different than the DA binding site). Methylphenidate basically stops the transporter, preventing DA reuptake and thus leading to increased synaptic availability of DA. Amphetamine Oral administration of clinically approved doses of the stimulant amphetamine, like methylphenidate, also blocks the transporters both for NE and DA (NETs and DATs), but in a different manner (Figures 11-30 through 11-32). Unlike methylphenidate and reuptake blocking drugs used for depression, amphetamine is a competitive inhibitor and pseudosubstrate for NETs

and DATs (Figure 11-32, top left), binding at the same site that the monoamines bind to the transporters, thus inhibiting NE and DA reuptake (Figure 11-32, top left). At the doses of amphetamine used for the treatment of ADHD, the clinical differences between the actions of amphetamine versus methylphenidate can be relatively small. However, at the high doses of amphetamine used by stimulant addicts, additional pharmacological actions of amphetamine are triggered. Following competitive inhibition of DATs (Figure 11-32, top left) amphetamine is actually transported as a hitch-hiker into the presynaptic DA terminal, an action not shared by methylphenidate or reuptake blocking drugs used for depression (Figure 11-32, top left). Once there in sufficient quantities, such as occurs at doses taken for abuse, amphetamine is also a competitive inhibitor of Mechanism of Action of Methylphenidate NE neuron C methylphenidate Figure 11-29C Mechanism of action of methylphenidate at norepinephrine neurons. Methylphenidate blocks the reuptake of norepinephrine (NE) into the terminal by binding at an allosteric site (i.e., different than the NE binding site). Methylphenidate basically stops the transporter, preventing NE reuptake and thus leading to increased synaptic availability of NE. the vesicular transporter (VMAT2) for both DA and NE (Figure 11-32, top right). Once amphetamine hitchhikes another ride into synaptic vesicles, it displaces DA there, causing a flood of DA release (Figure 11-32, bottom left). As DA accumulates in the cytoplasm of the presynaptic neuron, it causes the DATs to reverse directions, spilling intracellular DA into the synapse, and also opening presynaptic channels to further release DA in a flood into the synapse (Figure 1132, bottom right). These pharmacological actions of high-dose amphetamine are not linked to therapeutic action in ADHD but to reinforcement, reward, and euphoria in amphetamine abuse. Actions of highdose amphetamine, methamphetamine, and cocaine (another inhibitor of DATs), given orally in immediaterelease formulations, or intranasally, intravenously, or smoked, are discussed further in Chapter 13 on drug abuse. Amphetamine has a D- and an L-isomer (Figure 11-30). The D-isomer of amphetamine is more potent than the L-isomer for DAT binding, but D- and Lamphetamine isomers are more equally potent in their actions on NET binding. Thus, D-amphetamine preparations will have relatively more action on DATs

D,L-Amphetamine NET NET DAT DAT VMAT VMAT D-amphetamine L-amphetamine Figure 11-30 D,L-amphetamine. Amphetamine consists of two enantiomers, D and L; both racemic D,L-amphetamine and D-amphetamine are available as therapeutic options. D,L-amphetamine and D-amphetamine are both competitive inhibitors at norepinephrine transporters (NETs), dopamine transporters (DATs), and vesicular monoamine transporters (VMATs). D-amphetamine has greater potency for DAT binding than does the L enantiomer, while the D and L enantiomers are equipotent for NET binding. Lisdexamfetamine NET VMAT DAT lysine D-amphetamine Figure 11-31 Lisdexamfetamine. Lisdexamfetamine is the prodrug of D-amphetamine, linked to the amino acid lysine. It is only centrally active as D-amphetamine once it has been cleaved in the stomach into the active compounds D-amphetamine plus free L-lysine. than NETs; mixed salts of both D- and L-amphetamine will have relatively more action on NETs than Damphetamine but overall still more action on DATs than NETs (Figure 11-33). These pharmacological mechanisms of action of the stimulants come into play particularly Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment at lower therapeutic doses utilized for the treatment of ADHD. D-amphetamine also comes in a formulation linked to the amino acid lysine (lisdexamfetamine; Figure 11-31) which is not absorbed until slowly cleaved into active D-amphetamine in the stomach, and slowly, rather than rapidly, absorbed. A listing of the wide range of D,L amphetamine preparations is shown in Table 11-3, and those for D-amphetamine shown in Table 11-4. The Mysterious DAT Targeting the

dopamine transporter (DAT) is not like targeting any other site in psychopharmacology. There are at least three parts to solving the mystery of why there are so many different outcomes from targeting the same DAT, simply depending upon how you zero in on it. Targeting DATs can result in immediate therapeutic actions (in ADHD and daytime sleepiness), delayed therapeutic actions (in depression), immediate abuse (euphoria, high), and delayed addiction, all depending upon how the DAT is engaged: how fast, how long, and how much. Understanding the neurobiology of DATs and dopamine will not only unravel this mystery and solve the riddle of the curious properties of this site, but empower the prescriber to best engage this target for best outcomes for whatever clinical application is intended. First, we have discussed how engaging monoamine neurotransmitter transporters leads to delayed therapeutic actions in depression hypothetically linked to downstream molecular events such as neurotrophic factor production (discussed in Chapter 6 and illustrated in Figure 6-27 and in Chapter 7 and Figure 7-62). The immediate rise in dopamine levels (often accompanied by increasing norepinephrine levels from simultaneously blocking the NET) are not linked to antidepressant effects. Instead, DATs (and NETs) must be engaged at therapeutic levels more or less continuously, round the clock, so synaptic levels of neurotransmitter are sufficiently robust and sustained to trigger delayed downstream molecular events, usually taking a few weeks. Likely, these therapeutic actions may be linked to improvement of tonic dopamine neurotransmission that is theoretically deficient in depression. Second, engaging this same DAT can produce immediate onset of therapeutic effects in ADHD and in daytime sleepiness by attaining occupancy levels above a critical threshold, with therapeutic action that is immediately terminated as soon as DAT occupancy falls below this threshold (Figure 11-34A). This notion of a threshold for immediate therapeutic action onset and 473

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY capture the best way to attain, sustain, and drop below the threshold in just the exact manner desired. There are over two dozen versions of the two stimulant molecules methylphenidate and amphetamine now available for clinical use (Tables 11-1 through 11-4) and several more in development. Each version tries to capture the ideal drug delivery for the ideal DAT occupancy for a given patient type (e.g., Figure 11-34B). That usually takes the form of rapidly getting above threshold levels offset is also seen in another area of psychopharmacology, namely, for treatments of insomnia discussed in Chapter 10 and illustrated in Figure 10-41A. A similar idea is illustrated here, with a minimum threshold for ADHD therapeutic action, probably around 50–60% DAT occupancy (Figure 11-34). This property of DAT targeting for ADHD above a critical threshold is so prominent that it has spawned an entire industry of technologies in an attempt to 1 = competitive inhibition 2 = DAT transport of amphetamine Mechanism of Action of Amphetamine: The Yin and the Yang 3 = VMAT transport of amphetamine 5 = high DA opens channel and spills out 6 = high DA reverse transports DA out 4 = amphetamine displacement of dopamine 2 3 4 4 4 6 5 VMAT Figure 11-32 Mechanism of action of amphetamine at dopamine (DA) neurons. Amphetamine is a competitive inhibitor at the dopamine transporter (DAT), thus blocking DA from binding (1). This is unlike methylphenidate’s actions at DATs and NETs, which are not competitive. Additionally, since amphetamine is also a competitive inhibitor of VMAT (a property that methylphenidate lacks) it is actually taken into the DA terminal via DATs (2), where it can then be packaged into vesicles (3). At high levels, amphetamine will lead to the displacement of DA from the vesicles into the terminal (4). Furthermore, once a critical threshold of DA has been reached, DA will be expelled from the terminal via two mechanisms: the opening of channels to allow for a massive dumping of DA into the synapse (5) and the reversal of DATs (6). This fast release of DA will lead to the euphoric effect experienced after amphetamine use.

Amphetamine has these same actions at noradrenergic neurons.

Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment Table 11-3 D,L-Amphetamine formulations Formulation Brand names Duration Dosing Approval Immediate-release tablet Adderall 4–6 hrs Second dose at lunch Ages 3 and older Immediate-release tablet Evekeo 6 hrs Second dose at lunch Ages 3 and older Extended-release orally disintegrating tablets Adzenys XR-ODT 8–12 hrs, peak at 5 hrs Once daily in the morning Ages 6 and older Extended-release oral suspension Dyanavel XR 10–12 hrs, peak at 4 hrs Once daily in the morning Ages 6 to 17 Extended-release capsule Adderall XR 8–12 hrs, peak at 6–8 hrs Once daily in the morning Ages 6 and older Extended-release capsule Mydayis Up to 16 hrs Once daily in the morning Ages 13 and older Extended-release oral suspension Adzenys ER Not published Once daily in the morning Ages 6 and older Table 11-4 D-Amphetamine formulations Formulation Brand names Duration Dosing Approval Immediate-release tablet Zenzedi 4–5 hrs Second dose at lunch Ages 3 to 16 Immediate-release oral solution ProCentra (previously Liquadd) 4–6 hrs Second dose at lunch Ages 3 to 16 Extended-release capsule Dexedrine 6–8 hrs Once daily in the morning Ages 6 to 16 Lisdexamfetamine dimesylate capsule Vyvanse Up to 12 hrs, peak at 3.5 hrs Once daily in the morning Ages 6 to 17 and adults upon awakening in the morning, staying at this DAT occupancy level for as long as needed for a productive day, yet getting below threshold levels in time for bed. And to do this with once-daily dosing. Doing this too late means morning symptoms (Figure 11-34B); having it last too short a time means late afternoon and evening symptoms (Figure 11-34B); having this last too long a time means late afternoon and evening side effects and insomnia (Figure 11-34C). There is also a rebound phenomenon, in which evening serum levels drop too early and hyperactivity and insomnia ensue. Just as was discussed for hypnotic actions, the goal is not “too hot” (too long, too high, too fast), not “too cold” (too low, too short) but “just right” (Figure 11-34A), the ideal “Goldilocks” solution, more a goal than a perfectly executed reality. There is no “one size fits all” profile of stimulant delivery that fits every patient every day and no single technology that is ideal for all patients. For that reason, it can be prudent to search among the many options available for the best fit for an individual patient (see Tables 11-1 through 11-4). Do you want the effect to last 6 hours or 16 hours? Do you want greater or lesser effect in the evening hours before bedtime? Morning can be difficult for many with ADHD, so do you want rapid morning onset or even waking up with drug above threshold? All of these are currently attainable from available formulations (Tables 11-1 through 11-4). Different patients have different responses, and the same patient may wish different responses on different days to fit a flexible lifestyle. And all this because of the mysterious DAT and its threshold for therapeutic efficacy

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY and Figure 13-7). In fact, the more rapidly and completely the DATs are blocked, the more reinforcing and abusable a drug will be. This applies not only to methylphenidate, modafinil, and amphetamine as DAT blockers, but also to methamphetamine and cocaine that are also DAT blockers. Oral ingestion can get a DAT inhibitor to the brain, but not as fast as snorting nasally, and not as fast as intravenously, and certainly not as fast as smoking. High dosing especially by these other routes of administration provides complete, catastrophic, and sudden blockade of DATs. The rapid build-up of synaptic dopamine (Figure 11-35) is nothing like what is seen with more gradual, sustained, and lower levels of DAT occupancy (Figure 11-33). In fact, dopamine levels can build up so high that the DATs can actually be reversed to transport dopamine out of the presynaptic terminal to add to the in ADHD (and excessive daytime sleepiness). Likely these therapeutic actions may be linked to judicious and

controlled enhancement of phasic dopamine neurotransmission, along with a boost in tonic dopamine neurotransmission, both of which may be theoretically somewhat deficient in ADHD and sleepiness. One last piece of the puzzle. How can the DAT target that is therapeutic immediately for ADHD and sleepiness and with a delay for depression lead to problematic drug abuse rather than therapeutic use? This only makes sense if you are aware that the DAT functions very differently depending upon how fast, how completely, and how long you engage it (compare Figures 11-35 pulsatile action with Figure 11-33 sustained action). That is, rapid and high degrees of DAT occupancy cause euphoria and lead to abuse and addiction (Figure 11-35; see also Chapter 13 D >> L methylphenidate D = L amphetamine nucleus accumbens slow-dose stimulants OROS - methylphenidate, LA - methylphenidate, XR - D-methylphenidate, transdermal methylphenidate D-amphetamine spansules, XR - D,L mixed amphetamine salts, prodrug D-amphetamine (lisdexamfetamine) “Slow-Dose” Stimulants Amplify Tonic NE and DA Signals D >> L methylphenidate D > L amphetamine PFC D1 NET NE DAT DA VMAT2 VMAT2 NE neuron DA neuron 2A α + + + + + + + + + + + + + + + + + + D1 D2 DA VMAT2 DA neuron Figure 11-33 Slow-dose stimulants amplify tonic norepinephrine (NE) and dopamine (DA) signals. Hypothetically, whether a drug has abuse potential depends on how it affects the DA pathway. In other words, the pharmacodynamic and pharmacokinetic properties of stimulants affect their therapeutic as well as their potential abuse profiles. Extended-release formulations of oral stimulants, the transdermal methylphenidate patch, and the prodrug lisdexamfetamine are all considered “slow-dose” stimulants and may amplify tonic NE and DA signals, presumed to be low in ADHD. These agents block the norepinephrine transporters (NETs) in the prefrontal cortex and the DA transporters (DATs) in the nucleus accumbens. Hypothetically, the “slow-dose” stimulants occupy NETs in the prefrontal cortex (PFC) with slow enough onset, and for long enough duration, that they enhance tonic NE and DA signaling via α2A and D1 postsynaptic receptors, respectively, but they do not occupy DATs quickly or extensively enough in the nucleus accumbens to increase phasic signaling via D2 receptors. The latter hypothetically suggests reduced abuse potential.

Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment Figure 11-34 Dopamine transporter (DAT) occupancy levels and therapeutic effects. The therapeutic effects of DAT blockade are dependent upon attaining occupancy levels above a critical therapeutic threshold, with therapeutic action terminated as soon as occupancy falls below this threshold. The critical threshold of receptor occupancy for onset of therapeutic actions in ADHD is likely between 50% and 60%. Both the onset to achieving the threshold, and the duration of time above the threshold, are important for efficacy and tolerability. (A) Ideally, onset of achieving therapeutic DAT occupancy would be immediately upon waking, with levels maintained within the critical threshold throughout the day and dropping below the threshold in time for sleep. (B) Delayed onset of DAT blockade in the critical threshold can lead to morning symptoms, while inadequate duration of DAT blockade can cause evening symptoms. (C) If DAT blockade remains within the critical threshold for too long, this can result in evening side effects, notably insomnia. A drug concentration hours (taken daily) offset in time for sleep rapid morning onset 48 threshold for ADHD therapeutic effect B drug concentration hours (taken daily) too soon offset; late afternoon and evening symptoms delayed morning onsetmorning symptoms 48 threshold for ADHD therapeutic effect C drug concentration hours (taken daily) too offset; late, insomnia 48 threshold for ADHD therapeutic effect

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY long, but also how quickly the DAT is inhibited, all to maximize therapeutic effects in ADHD and minimize abuse and side effects (Figure 11-36 and Tables 111 through 11-4). The goal is to enhance phasic DA neurotransmission with low to moderate, continuous drug delivery (Figure 11-36, top), trying to increase mostly tonic DA firing and only judiciously to increase phasic DA firing, recognizing that this may be playing a bit with fire. In order not to get burned, as happens with pulsatile drug delivery in drug abuse situations (see Figure 11-36, bottom), to achieve prudent and therapeutic improvement of tonic and phasic DA neurotransmission without disastrous increases in phasic DA neurotransmission, leading to abuse and massive release of dopamine from sudden, complete, and catastrophic DAT blockade (discussed earlier in this chapter and illustrated in Figure 11-32, bottom right). So, understanding how a more gentle and prudent administration of DAT inhibition can be therapeutic whereas the same drug can be disastrous can allow the best judicious administration of a DAT inhibitor. Be careful, and don’t mess incorrectly with your DAT! Mystery solved. Slow-Release Versus Fast-Release Stimulants Based upon now having solved the mystery of the DAT, many drug delivery systems are not only designed to control how much DAT inhibition there is, and for how pulsatile stimulants oral immediate-release, intravenous, intranasal, smoked, D-amphetamine, D,L amphetamine salts, methylphenidate, D-methylphenidate, cocaine, methamphetamine amphetamine amphetamine Pulsatile Stimulants Amplify Tonic and Phasic NE and DA Signals methylphenidate methylphenidate nucleus accumbens PFC D1 D1 D1 D1 NET NE DAT NE neuron DA neuron 2A α 1 α 2A α α D1 D2 D1 D2 D1 D2 DA DA neuron + Figure 11-35 Pulsatile stimulants amplify tonic and phasic norepinephrine (NE) and dopamine (DA) signals. Hypothetically, whether a drug has abuse potential depends on how it affects the DA pathway. In other words, the pharmacodynamic and pharmacokinetic properties of stimulants affect their therapeutic as well as their potential abuse profiles. Immediate-release oral stimulants – similarly to intravenous, smoked, or snorted stimulants (which are considered pulsatile stimulants) – lead to a rapid increase in NE and DA levels through blockade of the norepinephrine transporters (NETs) in the prefrontal cortex (PFC) and the DA transporters (DATs) in the nucleus accumbens. Rapidly amplifying the phasic neuronal firing of DA in the nucleus accumbens is associated with euphoria and abuse. The abuse potential of immediate-release formulations of methylphenidate and amphetamine may be due to increased phasic as well as tonic DA signaling.

Pulsatile vs. Slow/Sustained Drug Delivery: Implications for Stimulants drug concentration dose DA firing A drug concentration dose dose dose dose DA firing B addiction, sustained delivery is what is wanted. Thus, controlled-release preparations for stimulants result in slowly rising, constant, steady-state levels of the drug (Figures 11-33, 11-34A; 11-35, top). Under those circumstances the firing pattern of DA will theoretically be mostly tonic, regular, and not at the mercy of fluctuating levels of DA. Some pulsatile firing is fine, especially when involved in reinforcing learning and salience (Figure 11-10). However, as seen in Figures 11-15 and 11-16, DA stimulation follows an inverted U-shaped curve, such that somewhat excessive DA will mimic the actions of DA in stress (Figure 11-14) and, at much higher doses, mimic drug abuse (Figure 11-36B). Thus, pulsatile drug administration that causes immediate release of DA, unlike controlledrelease preparations, could potentially lead to the highly reinforcing pleasurable effects of drug abuse, especially at high enough doses and rapid enough administration. For this reason, using immediate-release

stimulants, especially in adolescents and adults, is increasingly being avoided. Just as importantly, the “slow-dose” stimulants, shown in Figure 11-33, optimize the rate, the amount, and the length of time that a stimulant occupies not only DATs for therapeutic use in ADHD, but also exploits the slow-dose occupancy of NETs for therapeutic actions in ADHD. Best pharmacological use of stimulants in Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment Figure 11-36 Pulsatile versus slow and sustained drug delivery. The difference between stimulants as treatments and stimulants as drugs of abuse lies less in their mechanism of action and more in the route of administration and dose, and thus the onset and duration of dopamine transporter (DAT) blockade. (A) When using stimulants to treat a patient it may be preferable to obtain a slow-rising, constant, steady-state level of the drug. Under those circumstances the firing pattern of DA will be tonic, regular, and not at the mercy of fluctuating levels of DA. (B) While some pulsatile firing can be beneficial, especially when involved in reinforcing learning and salience, higher doses of DA will mimic the actions of DA in stress and mimic drug abuse at the highest doses. Unlike a constant administration of DA, pulsatile administration of DA may lead to the highly reinforcing pleasurable effects of drugs of abuse and lead to compulsive use and addiction. time time time time ADHD (and sleepiness) targets both NETs and DATs rather than raising the dose to get predominantly DAT effects, many of which will be unwanted. Optimization for ADHD means not only targeting DATs, but also targeting NETs to occupy enough of these NETs in the prefrontal cortex at a slow enough onset and a long enough duration of action to enhance tonic NE signaling there via α2A receptors (see discussion in Chapter 7 and Figure 7-33 for how NET inhibition leads to enhanced NE action). NET inhibition can also increase tonic DA signaling in the prefrontal cortex via D1 receptors, as explained in Chapter 7 and illustrated in Figure 7-33. This allows good therapeutic effects in ADHD while occupying carefully a lower number of mysterious DAT targets, especially in the nucleus accumbens, so as not to increase phasic signaling there via D2 receptors (Figures 11-35 and 11-36). In summary, it appears that ADHD patients have their therapeutic improvement by stimulants at the mercy of how quickly, how much, and how long stimulants occupy NETs and DATs. When this is done in an ideal manner with slow onset, robust but subsaturating levels of transporter blockade, together with a long duration of action before declining and wearing off, the patient ideally benefits with improved ADHD symptoms, hours of relief, and no euphoria (Figures 11-34 and 11-36). 479

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Noradrenergic Treatment of ADHD Atomoxetine Atomoxetine (Figure 11-37) is a selective norepinephrine reuptake inhibitor (NRI). Sometimes called NET inhibitors, the selective NRIs have known antidepressant properties (discussed in Chapter 7). In terms of their mechanism of therapeutic action in ADHD, it is the same as just discussed for stimulants acting at the NETs here in Chapter 11, and as previously discussed for drugs used to treat depression in Chapter 7 and illustrated in Figure 7-33. Blocking NETs in the prefrontal cortex increases Comparing the Molecular Actions of Atomoxetine and Bupropion DAT NDRIs NET NE neuron DA neuron NRIs NET Figure 11-37 Comparing the molecular actions of atomoxetine and bupropion. Atomoxetine is a selective norepinephrine reuptake inhibitor (NRI), while bupropion is a norepinephrine– dopamine reuptake inhibitor (NDRI). Both agents block the norepinephrine transporters (NETs) in the prefrontal cortex, which leads to an increase in both norepinephrine (NE) and dopamine (DA) there (because NETs also transport dopamine). NDRIs also block the dopamine transporters (DATs), which are not present in the prefrontal cortex but are present in the nucleus accumbens. both DA and NE in the prefrontal cortex (Figure 11-38) and is why NET inhibitors are thought to work in ADHD. However, since there are few NE neurons and NETs in nucleus accumbens, inhibiting NET does not lead to an increase in either NE or DA there

(Figure 11-38) and is why NET inhibitors are thought not to have reinforcing, abuse, or addiction potential. Bupropion is a weak NRI and also a weak DAT inhibitor known as a norepinephrine–dopamine reuptake inhibitor (NDRI), and was previously discussed as a treatment for depression in Chapter 7 and illustrated in Figures 7-34 through 7-36; see also Figure 11-37). Several tricyclic antidepressants (TCAs) have notable NRI actions, such as desipramine and nortriptyline. All of these agents with NRI properties have been utilized in the treatment of ADHD, with varying amounts of success, but only atomoxetine is well-investigated and approved for this use in children and adults. Atomoxetine's hypothetical actions in ADHD patients with stress and comorbidity states, presumably linked to excessive and phasic DA and NE release, are shown conceptually by comparing the untreated states in Figures 11-11 and 11-12 with the changes that theoretically follow chronic treatment with atomoxetine in Figure 11-39. That is, ADHD linked to conditions that are associated with chronic stress and comorbidities is theoretically caused by overly active NE and DA circuits in the prefrontal cortex, resulting in an excess of phasic NE and DA activity (Figure 11-13). When slow onset, long duration, and essentially perpetual NET inhibition occurs in the prefrontal cortex due to atomoxetine, this theoretically restores tonic postsynaptic D1 and α2A-adrenergic signaling, downregulates phasic NE and DA actions, and desensitizes postsynaptic NE and DA receptors (Figure 11-39). The possible consequence of this is to reduce stress as ADHD symptoms are improved. If so, decreases in ADHD symptoms could potentially be accompanied by decreases in anxiety, depression, and heavy drinking. Unlike stimulant use, where the therapeutic actions are at the mercy of plasma drug levels and momentary NET/ DAT occupancies, actions from long-term NRI actions give 24-hour symptom relief, in much the same manner as do SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin–norepinephrine reuptake inhibitors) for the treatment of depression and anxiety. Selective NRIs generally have smaller effect sizes for reducing ADHD symptoms than stimulants in short-term trials, especially in patients without comorbidity. However, NRIs are not necessarily inferior in ADHD patients who

Atomoxetine in ADHD with Weak Prefrontal NE and DA Signals nucleus accumbens - no action prefrontal cortex NE neuron DA neuron VMAT2 VMAT2 NET atomoxetine NE DAT DA D1 2A α + + + + + + + + + NET inhibitors atomoxetine (NRI), reboxetine (NRI), bupropion (NDRI), venlafaxine (SNRI), duloxetine (SNRI), desvenlafaxine (SNRI), milnacipran (SNRI), desipramine (TCA), nortriptyline (TCA) Chronic Treatment with Atomoxetine in ADHD with Excessive Prefrontal NE and DA Signals prefrontal cortex excessive NE and DA signals stress stress ADHD anxiety substance abuse chronic treatment with atomoxetine NE neuron DA neuron VMAT2 VMAT2 NET atomoxetine NE DA D1 2A α + + + + + + + + + RESPONSE Figure 11-39 Chronic treatment with atomoxetine in ADHD with excessive signals. ADHD linked to conditions that are associated with chronic stress and comorbidities is theoretically caused by overly active NE and DA circuits. Continuous blockade of NETs could restore tonic postsynaptic D1 and α2Aadrenergic signaling, downregulate phasic NE and DA actions, and desensitize postsynaptic NE and DA receptors. Figure 11-38 Atomoxetine in ADHD with weak prefrontal norepinephrine (NE) and dopamine (DA) signals. Through its blockade of norepinephrine transporters (NETs), atomoxetine causes NE and DA levels to increase in the prefrontal cortex, where inactivation of both of these neurotransmitters is largely due to NETs (on the left). At the same time, the relative lack of NETs in the nucleus accumbens prevents atomoxetine from increasing NE or DA levels in that brain area, thus reducing the risk of abuse (on the right). Other NET inhibitors would be expected to have the same effects. DA neuron VMAT2 DA D1 D2 + + have not been previously treated with stimulants, nor in ADHD patients who have been treated long term (more than 8–11 weeks). NRIs may actually be preferred to stimulants in patients

with complex comorbidities, side effects, or lack of response to stimulants. Alpha-2A-Adrenergic Agonists Norepinephrine receptors are discussed in Chapter 6 and illustrated in Figures 6-14 through 6-16. There are numerous subtypes of α-adrenergic receptors, from presynaptic autoreceptors, generally of the α2A subtype (Figure 6-14) to postsynaptic α2A, α2B, α2C, and α1 subtypes α1A, α1B, and α1D (Figures 6-14 through 6-16). Alpha-2A receptors are widely distributed throughout the central nervous system, with high levels in the cortex and locus coeruleus. These receptors are thought to be the primary mediators of the effects of NE in the prefrontal cortex, regulating symptoms of inattention, hyperactivity, and impulsivity in ADHD. Alpha-2B receptors are in high concentrations in the thalamus and may be important in mediating sedating actions of NE, while α2C receptors are densest in striatum. Alpha-1 receptors generally have opposing actions to α2 receptors, with α2 mechanisms predominating when NE release is low or moderate (i.e., for normal attention), but with α1 mechanisms predominating at NE synapses when NE release is high (e.g., associated with stress and comorbidity) and contributing to cognitive impairment. Thus, selective NRIs at low doses will first increase activity at α2A 481

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY postsynaptic receptors to enhance cognitive performance, but at high doses may swamp the synapse with too much NE and cause sedation, cognitive impairment, or both. Patients with these responses to selective NRIs may benefit from lowering the dose. Alpha-2-adrenergic receptors are present in high concentrations in the prefrontal cortex, but only in low concentrations in the nucleus accumbens. There are two direct-acting agonists for α2 receptors used to treat ADHD, guanfacine (Figure 11-40) and clonidine (Figure 11-41). Guanfacine is relatively more selective for α2A receptors (Figure 11-40). It has been formulated into a controlled-release product, guanfacine ER, that allows once-daily administration, and lower peak-dose side effects than immediate-release guanfacine. Only the controlled-release version of guanfacine is approved for treatment of ADHD. Clonidine is a relatively nonselective agonist at α2 receptors, with actions on α2A, α2B, and α2C receptors (Figure 11-41). In addition, clonidine has actions on imidazoline receptors, thought to be responsible for some of clonidine's sedating and hypotensive actions (Figure 11-41). Although the actions of clonidine at α2A receptors exhibit therapeutic potential for ADHD, its actions at other receptors may increase side effects. Clonidine is approved for the treatment of hypertension, but only the controlledrelease version of clonidine is approved for treatment of Guanfacine α2A Figure 11-40 Guanfacine. Guanfacine is a selective α2A receptor agonist. Specifically, guanfacine is 15–60 times more selective for α2A receptors than for α2B and α2C receptors. ADHD. Both clonidine and guanfacine, especially in the controlled-release formulations, are used "off-label" for the treatment of conduct disorder, oppositional defiant disorder, and Tourette syndrome. Unlike clonidine, guanfacine is 15–60 times more selective for α2A receptors than for α2B and α2C receptors. Additionally, guanfacine is 10 times weaker than clonidine at inducing sedation and lowering blood pressure, yet it is 25 times more potent in enhancing prefrontal cortical function. The therapeutic benefits of both clonidine and guanfacine are hypothetically related to direct effects on postsynaptic receptors in the prefrontal cortex, which lead to the strengthening of network inputs, and to behavioral improvements, as seen in Figures 11-42 and 11-43. Who are the best candidates for monotherapy with an α2 agonist? Hypothetically, the symptoms of ADHD could be caused in some patients by NE levels being low in the prefrontal cortex, without additional impairments in DA neurotransmission (Figure 11-43A). This would lead to scrambled signals lost within the background noise, which could be seen behaviorally as hyperactivity, impulsivity, and inattention (Figure 11-43A). In this instance, treatment with a selective α2A agonist would lead to an increased signal via direct stimulation of

Clonidine α α 2A 2B α 2C imidazoline Figure 11-41 Clonidine. Clonidine is an α2 receptor agonist. It is nonselective and thus binds to α2A, α2B, and α2C receptors. Clonidine also binds to imidazoline receptors, which contributes to its sedating and hypotensive effects.

The Mechanism of Action of Clonidine and Guanfacine and How They Affect the Three Alpha-2 Receptors prefrontal cortex NE neuron DA neuron sedation hypotension 2B α NET sedation 2C α guanfacine

clonidine 2A α 2A α sedation hypotension + imidazoline receptor + + + Effects of an Alpha-2A Agonist in ADHD PFC strength of output VMPFC DA concentration noise signal NE concentration sit still behave pay attention hyperactivity impulsivity inattention A PFC strength of output VMPFC noise signal NE concentration sit still behave pay attention hyperactivity impulsivity inattention B Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment Figure 11-42 Mechanism of action of clonidine and guanfacine. Alpha2-adrenergic receptors are present in high concentrations in the prefrontal cortex, but only in low concentrations in the nucleus accumbens. There are three types of α2 receptors: α2A, α2B, and α2C. The most prevalent subtype in the prefrontal cortex is the α2A receptor. Alpha-2B receptors are mainly located in the thalamus and are associated with sedative effects. Alpha-2C receptors are located in the locus coeruleus, with few in the prefrontal cortex. Besides being associated with hypotensive effects, they also have sedative actions. In ADHD, clonidine and guanfacine – by stimulating postsynaptic receptors – can increase NE signaling to normal levels. The lack of action at postsynaptic DA receptors parallels their lack of abuse potential. DA D1 D2 + + Figure 11-43 Effects of an α2A agonist in ADHD. (A) The symptoms of ADHD could hypothetically be due to low norepinephrine (NE) levels in the prefrontal cortex (PFC), without additional impairments in dopamine (DA) neurotransmission. The resulting scrambled signals may manifest as hyperactivity, impulsivity, and inattention. (B) Treatment with a selective α2A agonist would lead to increased signal via direct stimulation of postsynaptic receptors, resulting in an increased ability to sit still and focus. VMPFC: ventromedial prefrontal cortex. ADHD: Hypothetically Low Signals Due to Low NE PFC strength of output NE low - signal reduced DA optimized - noise reduced Treatment with Alpha-2A Agonist PFC strength of output DA concentration NE optimized - signal enhanced DA optimized - noise reduced 483

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY postsynaptic receptors, and this would translate into the patient being able to focus, sit still, and behave adequately (Figure 11-43B). There is currently no way to identify these patients in advance, other than by an empiric trial of guanfacine ER. Patients suffering from ADHD and oppositional symptoms can be argumentative, disobedient, aggressive, and exhibit temper tantrums (Figures 11-8 and 11-44A). These behaviors are hypothetically linked to very low levels of NE and low levels of DA in the ventromedial prefrontal cortex (VMPFC), thus leading to much reduced signal and increased noise (Figure 11-44A). While treatment with a stimulant will improve the situation by reducing the noise, it would not solve any strong hypothetical NE deficiencies (Figure 1144B), therefore only partially improving behavior. How to Treat ADHD and Oppositional Symptoms ADHD and Oppositional Symptoms: Hypothetically Very Low Signals in VMPFC PFC strength of output PFC strength of output VMPFC noise signal NE concentration behave cooperate temper tantrums argumentative disobedient aggressive NE very low - signal much reduced DA low - noise increased A Treatment: Stimulant PFC strength of output PFC strength of output VMPFC noise signal NE concentration behave cooperate temper tantrums argumentative disobedient aggressive NE still low - signal still reduced DA optimized - noise

reduced B Treatment: Augment Stimulant with Alpha-2A Agonist PFC strength of output PFC strength of output VMPFC noise signal NE concentration behave cooperate temper tantrums argumentative disobedient aggressive NE optimized - signal increased DA optimized - noise reduced C Augmenting a stimulant with an α2A agonist (Figure 11-44C) could hypothetically solve the problem by optimizing the levels of NE, thus enhancing the signal, in the presence of an already optimized DA output. Behaviorally, this could hypothetically result in a patient cooperating and behaving appropriately. Guanfacine ER has been approved as an augmenting agent for patients inadequately responsive to stimulants, and may be especially helpful in patients with oppositional symptoms. Future Treatments for ADHD There are ever-evolving new technologies for drug delivery of amphetamine and methylphenidate and more of these are in development, partly because they allow customization of the duration of desired therapeutic Figure 11-44 How to treat ADHD and oppositional symptoms. Argumentative, disobedient, and aggressive behaviors are often seen in patients suffering from ADHD and oppositional symptoms. (A) These behaviors could theoretically be due to very low levels of norepinephrine (NE) and low levels of dopamine (DA) in the ventromedial prefrontal cortex (VMPFC), leading to much reduced signal and increased noise. (B) While treatment with a stimulant may reduce the noise, it will not solve the strong NE deficiencies, therefore only partially improving behavior. (C) The augmentation of a stimulant with an α2A agonist could optimize the levels of NE, thus enhancing the signal in the presence of an already optimized DA output. DA concentration DA concentration DA concentration

Viloxazine ER 5HT2B NET 5HT2C Figure 11-45 Viloxazine ER. Viloxazine is an inhibitor of the norepinephrine transporter (NET) and also has actions at serotonin 2B (5HT2B) and 5HT2C receptors. A controlled-release formulation is in late-stage clinical development for ADHD. action, and partially because they are patentable and commercializable. One newer aspect of controlled-release formulations is the potential to make them in a matrix that resists attempts to powderize for inhaling, snorting, smoking, or injecting. A selective NRI called viloxazine (Figure 11-45), once marketed abroad for the treatment of depression but never marketed in the US, has been repurposed in a controlled-release formulation for use in ADHD, and is now in late-stage clinical development for ADHD. Chapter 11: Attention Deficit Hyperactivity Disorder and Its Treatment The DAT inhibitor mazindol, once approved for appetite suppression, is in testing and so is a triple (5HT– NE–DA) reuptake inhibitor centanafadine. SUMMARY ADHD has core symptoms of inattentiveness, impulsivity, and hyperactivity, linked theoretically to specific malfunctioning neuronal circuits in the prefrontal cortex. ADHD can also be conceptualized as a disorder of dysregulation of norepinephrine and dopamine in the prefrontal cortex, including some patients with deficient norepinephrine and dopamine and others with excessive norepinephrine and dopamine. Treatments theoretically return patients to normal efficiency of information processing in prefrontal circuits. There are differences between children and adults with ADHD, and special considerations exist for how to treat these two populations. The mechanisms of action, both in terms of pharmacodynamics and pharmacokinetics, for stimulant treatments of ADHD are discussed in detail. The goal is to amplify tonic but not phasic norepinephrine and dopamine actions in ADHD by controlling the rate of stimulant drug delivery, the degree of transporter occupancy, and the duration of transporter occupancy. Theoretical mechanisms of action of selective norepinephrine reuptake inhibitors such as atomoxetine and their possible advantages in adults with chronic stress and comorbidities are discussed. Actions of α2Aadrenergic agonists are also presented. 485

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