Chapter 12

Attention deficit hyperactivity disorder and its treatment

Attention deficit hyperactivity disorder (ADHD) is increasingly being seen not just as a disorder of attention, nor just as a disorder of children. Paradigm shifts are altering the landscape for treatment options across the full range of ADHD symptoms, from inattention to impulsivity. 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 stimulants and nonstimulants in ADHD will also be explored. 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 and the various symptoms and comorbidities of ADHD, and how these are linked to effective psychopharmacologic treatments. The goal of this chapter is to acquaint the reader with ideas about the clinical and biological aspects of attention, impulsivity, and hyperactivity, also covering some of the aspects involved in treating adults with this disorder. 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 12-1). It is currently hypothesized that all these symptoms arise in part from abnormalities in various circuits involving the prefrontal cortex (Figures 12-2 through 12-8). Specifically, the most prominent symptoms of inattention in ADHD, better known as executive dysfunction and as the inability to sustain attention and thus to solve problems, are hypothetically linked to inefficient information processing in the dorsolateral prefrontal cortex (DLPFC) (Figures 12-2, 12-3, 12-7). 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 magnetic resonance imaging (fMRI) brain scanner (explained in Figure 12-3). Problems activating this part of the brain cut across many psychiatric disorders that share the symptom of executive dysfunction, not just ADHD but also including schizophrenia (discussed in Chapter 4), major depression (discussed in Chapter 6), mania (discussed in Chapter 6), anxiety (discussed in

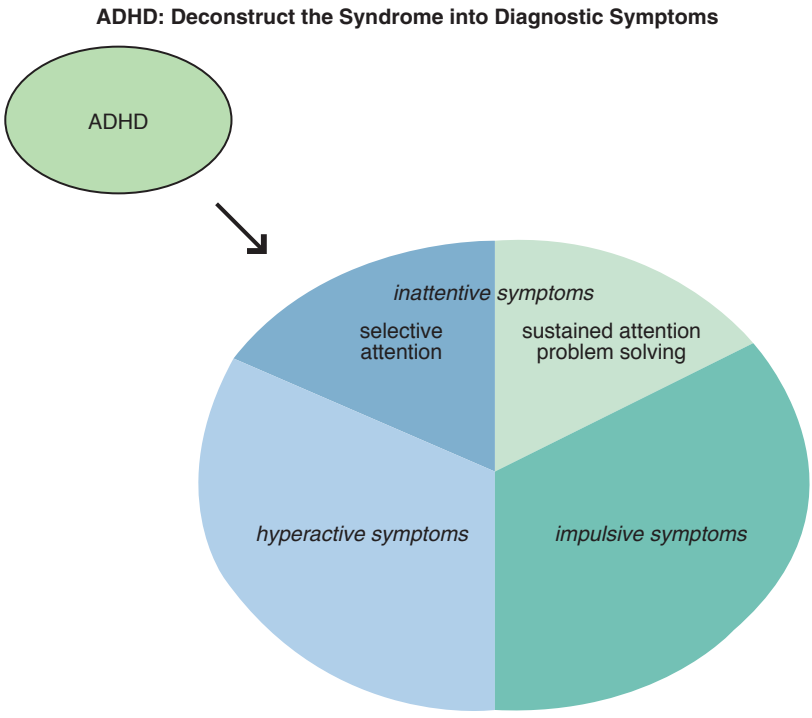

Figure 12-1. Symptoms of ADHD. There are three major categories of symptoms associated with attention deficit hyperactivity disorder (ADHD): inattention, hyperactivity, and impulsivity. Inattention itself can be divided into difficulty with selective attention and difficulty with sustained attention and problem solving.

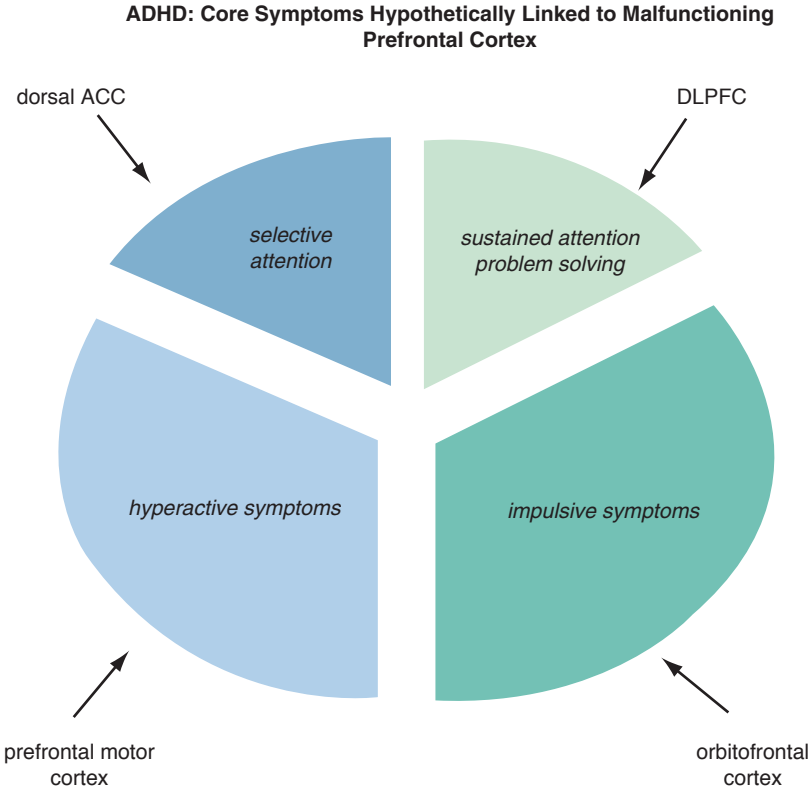

Figure 12-2. Matching ADHD symptoms to circuits. Problems with selective attention are believed to be linked to inefficient information processing in the dorsal anterior cingulate cortex (dACC), while problems with sustained attention are linked to inefficient information processing in the dorsolateral prefrontal cortex (DLPFC). Hyperactivity may be modulated by the prefrontal motor cortex and impulsivity by the orbitofrontal cortex (OFC).

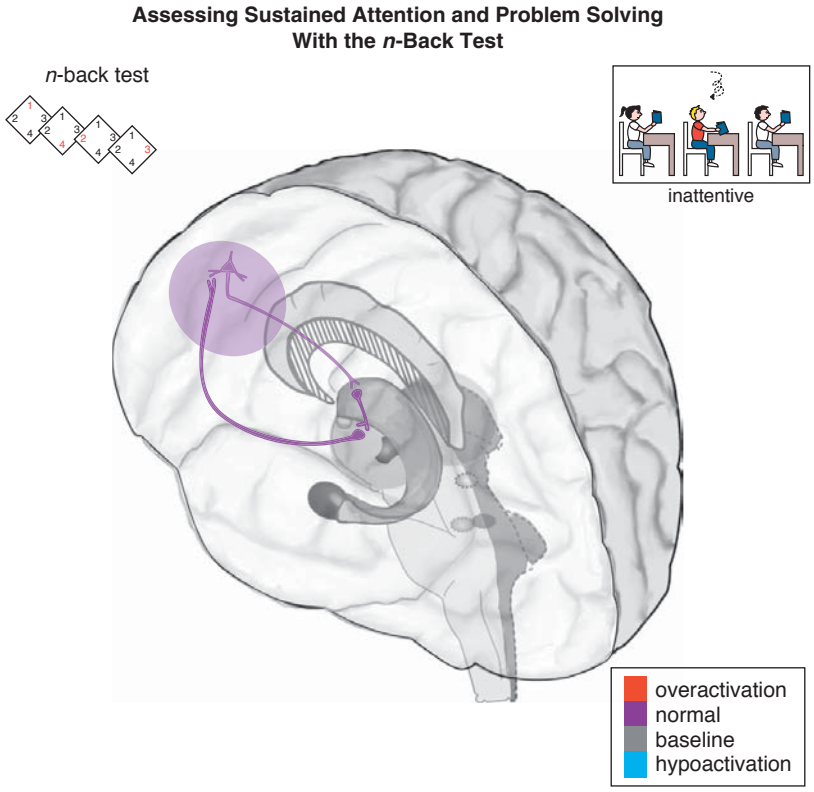

Figure 12-3. Sustained attention and problem solving: the *n*-back test. Sustained attention is hypothetically modulated by a cortico-striato-thalamo-cortical (CSTC) loop that involves the dorsolateral prefrontal cortex (DLPFC) projecting to the striatal complex. Inefficient activation of the DLPFC can 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, and 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.

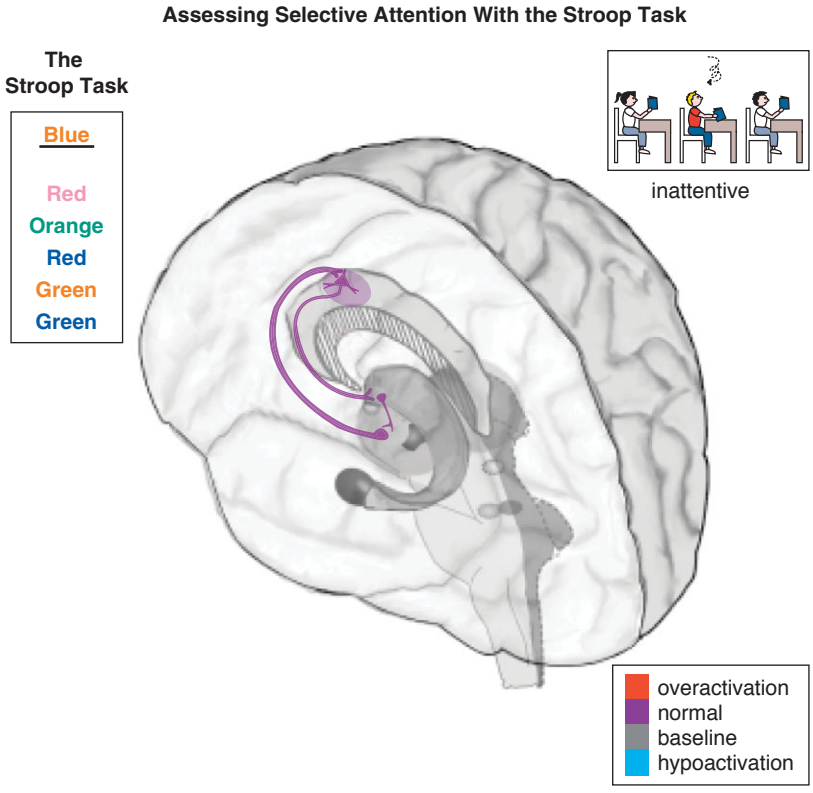

Figure 12-4. Selective attention: the Stroop task. Selective attention is hypothetically modulated by a cortico-striato-thalamo-cortical (CSTC) loop arising from the dorsal anterior cingulate cortex (dACC) and projecting to the striatal complex, then the thalamus, and back to the dACC. Inefficient activation 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 with which a word is written, instead of saying the word itself. In the present case, for example, the word "blue" is written in orange. The correct answer is therefore "orange," while "blue" is the incorrect choice.

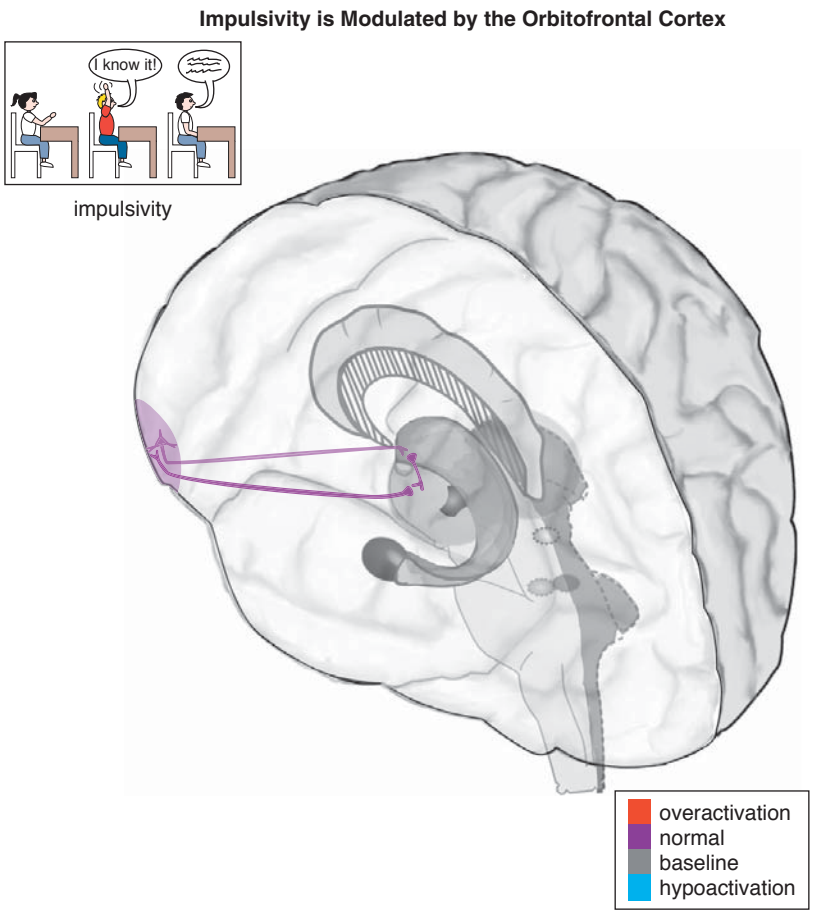

Figure 12-5. Impulsivity. Impulsivity is associated with a cortico-striato-thalamo-cortical (CSTC) loop that involves the orbitofrontal cortex (OFC), the striatal complex, and the thalamus. Examples of impulsive symptoms in ADHD include talking excessively, blurting things out, not waiting one's turn, and interrupting.

Chapter 9), pain (discussed in Chapter 10), and disorders of sleep and wakefulness (discussed in Chapter 11). One can see how inefficient information processing in this particular DLPFC circuit when put under a cognitive "load" can be associated with the same symptom in many different psychiatric disorders. This is why diagnosis in psychiatry is now moving from describing categorical syndromes that mix together many symptoms (as in the DSM and ICD), towards characterizing single symptom domains such as executive dysfunction that cut across many psychiatric disorders, sometimes called Research Domain Criteria (RDoC) for future diagnostic schemes that are set up to better correlate with neuroimaging and genetic findings.

Another symptom of ADHD is *selective* inattention, or not being able to focus, and thus differing from the executive dysfunction described above. The symptom of difficulty focusing is hypothetically linked to inefficient information processing in a different brain area, namely the dorsal anterior cingulate cortex (dACC) (Figures 12-2, 12-4, 12-7). The dACC can be activated by tests of selective attention, such as the Stroop test (explained in Figure 12-4). ADHD patients may either fail to activate the dACC when they should be focusing their attention, or they activate this part of the brain very inefficiently and only with great effort and easy fatigability.

Other areas of prefrontal cortex that are hypothetically not functioning efficiently in ADHD are the orbitofrontal cortex (OFC), linked to symptoms of impulsivity (Figures 12-2, 12-5, 12-7) and the supplementary motor area, linked to symptoms of motor hyperactivity (Figures 12-2, 12-6, 12-7). The OFC is hypothetically linked to a wide variety of symptoms

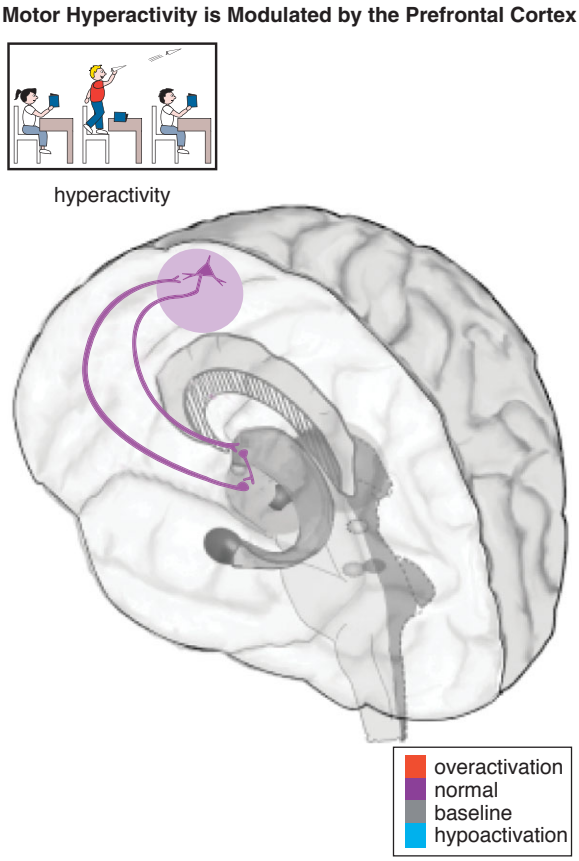

Figure 12-6. Hyperactivity. Motor activity, such as hyperactivity and psychomotor agitation or retardation, can be modulated by a cortico-striato-thalamo-cortical (CSTC) loop from the prefrontal motor cortex to the putamen (lateral striatum) to the thalamus and back to the prefrontal motor cortex. Common 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.

that cut across several psychiatric conditions, including impulsivity in ADHD (Figures 12-2, 12-5, 12-7), 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 (discussed in Chapter 14). Impulsive symptoms in other psychiatric conditions commonly comorbid with ADHD are also hypothetically related to the orbitofrontal cortex, such as conduct disorder, oppositional defiant disorder, and bipolar disorder (Figure 12-8). Impulsivity is discussed extensively in Chapter 14 (see Tables 14-1 through 14-8 and Figures 14-1 through 14-5).

ADHD as a disorder of inefficient "tuning" of the prefrontal cortex by dopamine and norepinephrine

ADHD patients generally cannot activate prefrontal cortex areas appropriately in response to cognitive tasks of attention and executive functioning. Some studies suggest that this is because dopamine (DA) and norepinephrine (NE) dysregulation in ADHD prevents the normal "tuning" of pyramidal neurons in the prefrontal cortex. In the case of DA and NE neurons, their normal firing at baseline is considered slow and "tonic," stimulating a few receptors on postsynaptic neurons and allowing for optimal signal transmission and downstream neuronal firing (Figure 12-9). Modest levels of NE release will hypothetically improve prefrontal cortical function by stimulating postsynaptic α_{2A} receptors, but high levels of NE release will lead to impaired working memory when α_1 and β_1 receptors are also recruited (Figure 12-9). Similarly, modest levels of DA will first stimulate D_3 receptors, as these are more sensitive to DA than D_1 or D_2 receptors (Figure 12-9). Hypothetically, low to moderate, but not high, levels of D_1 receptor stimulation is beneficial to optimizing prefrontal cortical functioning.

Dopamine neurons in particular can also exhibit bursts of firing, called phasic (Figure 12-10). Phasic DA release is thought to reinforce learning and reward conditioning, providing the motivation to pursue naturally rewarding experiences such as education, recognition, career development, enriching social and family connections, etc. When the phasic DA system is hijacked by drugs, it can induce uncontrolled DA firing that reinforces the reward of drug abuse, and lead to compulsive behaviors such as mindless self-destructive drug seeking (discussed in Chapter 14). Thus, finely tuning the DA reward pathway in the nucleus accumbens and its connections to the amygdala and prefrontal cortex by attaining a low level of phasic firing in relation to tonic firing will theoretically lead to proper functioning of this complex system.

In ADHD, imbalances in NE and DA circuits in the prefrontal cortex hypothetically cause inefficient information processing in prefrontal circuits, and thus the symptoms of ADHD (as shown for *circuits* in Figures 12-2 through 12-8). At the level of NE

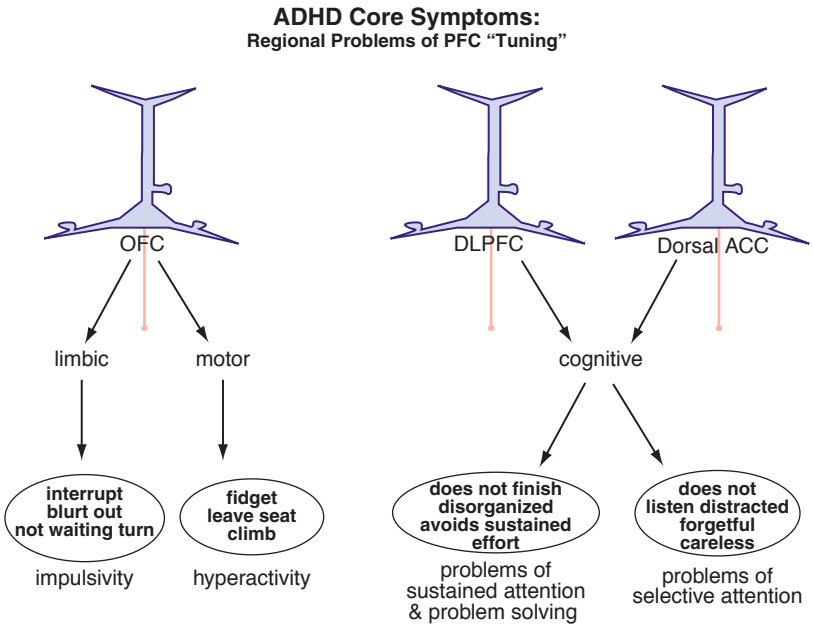

Figure 12-7. ADHD: out-of-tune prefrontal cortex. Different brain areas are hypothetically important in the symptoms of ADHD. Alterations within the orbitofrontal cortex (OFC) are hypothesized to lead to problems with impulsivity or hyperactivity. Inadequate tuning of the DLPFC or the dACC can respectively lead to sustained or selective attentive symptoms. It is becoming increasingly clear that dysfunction in specific brain areas leads to specific symptoms, such that abnormalities in the orbitofrontal–limbic motivation networks have been observed in children with conduct disorder, while aberrations in the dorsolateral cognitive network have been observed in children with problems of sustained attention.

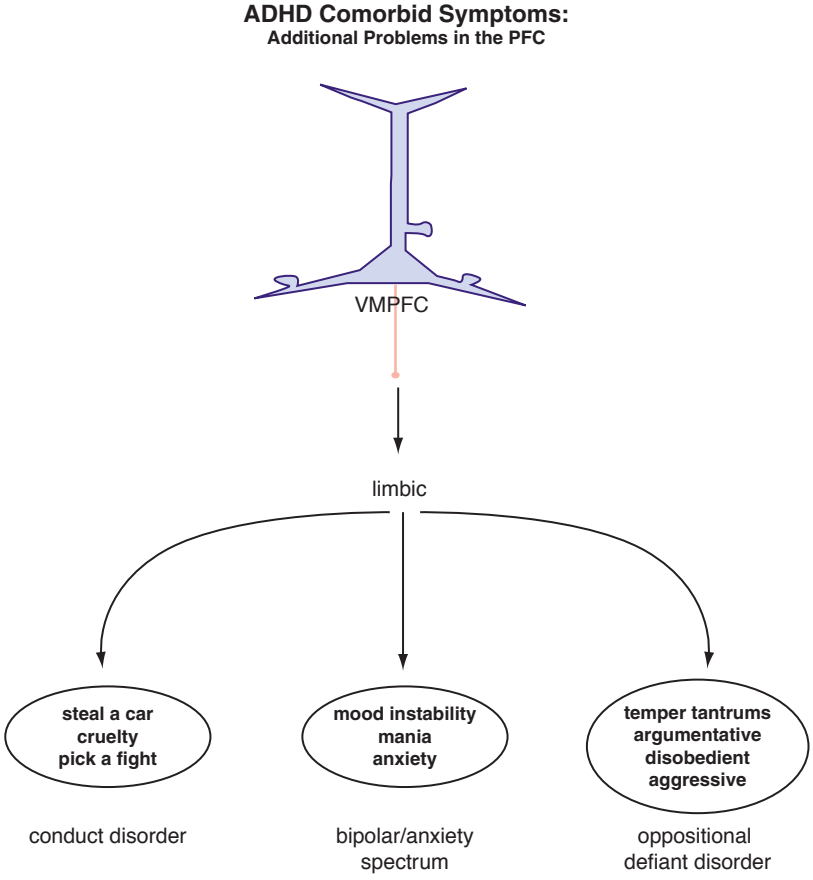

Figure 12-8. ADHD and comorbid symptoms. The comorbidities associated with ADHD are often the result of similar or additional dysfunctions within the prefrontal cortex–limbic network. Many mood disorders are comorbid with ADHD both in children and in adults, and it has been suggested that the symptoms in adults might be most disabling if the comorbidities were already present in the child. This emphasizes the importance of treating all the symptoms in the younger population of ADHD patients in order to maximize their chances of a "regular" adult life. VMPFC, ventromedial prefrontal cortex.

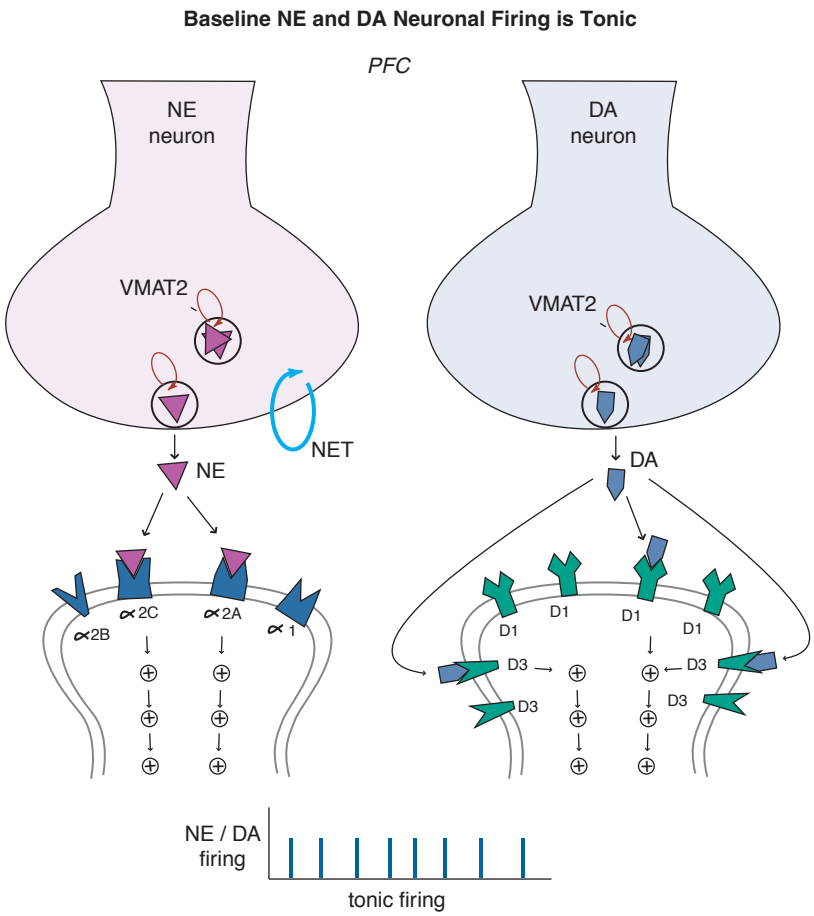

Figure 12-9. Baseline tonic firing. Modulation of prefrontal cortical function, and therefore regulation of attention and behavior, relies on the optimum release of dopamine (DA) and norepinephrine (NE). Under normal conditions, released NE and DA in the prefrontal cortex stimulate a few receptors on postsynaptic neurons allowing for optimal signal transmission and neuronal firing. At modest levels, NE can improve prefrontal cortical function by stimulating postsynaptic α_{2A} receptors, but will lead to impaired working memory at high levels when α_1 and β_1 receptors are also recruited. Similarly, modest levels of DA will first stimulate D_3 receptors as these are more sensitive to DA than D_1/D_2 receptors. Low to moderate, but not high, levels of D_1 receptor stimulation can be beneficial to prefrontal cortical functioning. In the case of both DA and NE systems, moderation is certainly key.

and DA *synapses* in the prefrontal cortex, deficient signaling in prefrontal cortical DA and NE pathways is reflected by decreased neurotransmission and thus reduced stimulation of postsynaptic receptors (Figure 12-11). Agents that can lead to increased release of these two neurotransmitters or increased tonic firing of these neurons will be hypothetically beneficial in patients with ADHD by bringing prefrontal activity back to optimal levels. On the other hand, ADHD can also be hypothetically associated with excessive signaling in prefrontal cortical DA and NE pathways, particularly in adolescents and adults (Figure 12-12). That is, stress can activate NE and DA circuits in the prefrontal cortex, leading to high levels of DA and NE release, and thus cause an excess of phasic NE and DA firing (Figure 12-12). This excessive NE and DA neurotransmission may be the underpinning of the development of drug and alcohol abuse, impulsivity, inattention and anxiety, all comorbid with ADHD, particularly in adolescents and adults.

So, is the prefrontal cortex out of tune when NE and DA are too high or too low? The answer seems to be that either too much or too little stimulation by NE or DA can cause inefficient information processing, because for the prefrontal cortex to work properly, cortical pyramidal neurons need to be tuned, meaning that moderate stimulation of α_{2A} receptors by NE and D_1 receptors by DA is required, neither too high nor too low. 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. Pyramidal cell function is optimal at the top of this inverted U-shaped curve, when stimulation of both α_{2A} and D_1 receptors is moderate (Figure 12-13). If stimulation at α_{2A} and D_1 receptors is too low (left side of Figure 12-13), all

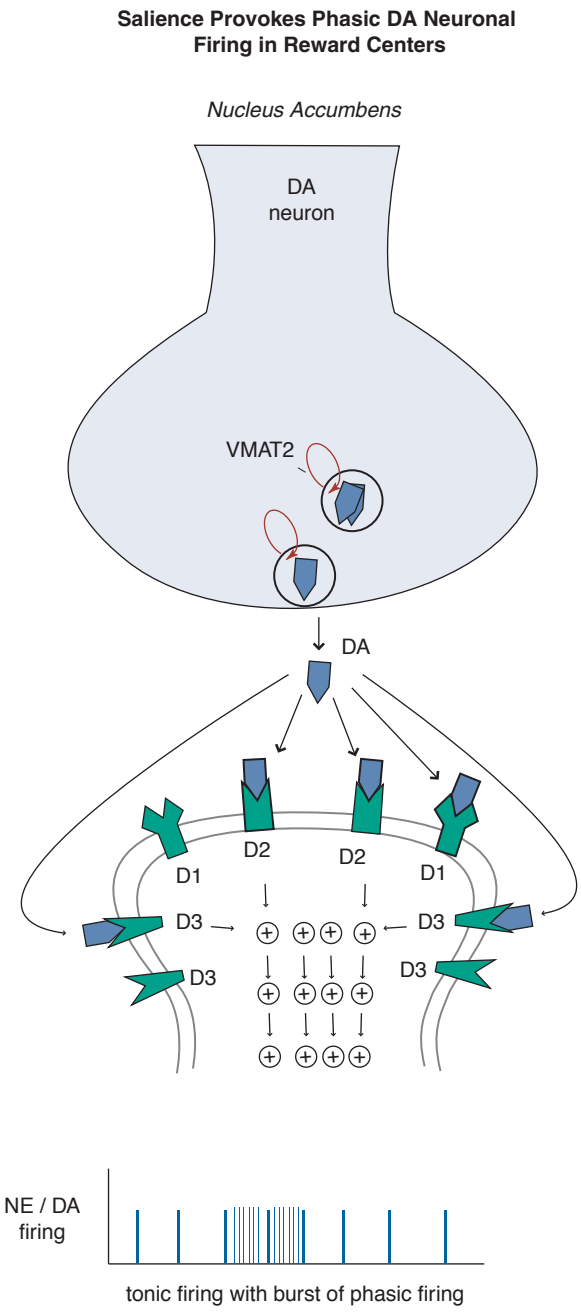

Figure 12-10. Salience-provoked phasic firing. While tonic firing, as seen in the prefrontal cortex, is often preferred in neuronal systems, a little bit of phasic firing of DA neurons in the nucleus accumbens can be a good thing. Phasic firing will lead to bursts of DA release, and when this happens 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 however is out of bounds, 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.

incoming signals are the same, preventing a person from focusing on one single task (unguided attention). When stimulation is too high (right side of Figure 12-13) the signals get scrambled as additional receptors are recruited, again misguiding a person's attention. A balanced, moderate stimulation of α_{2A} and D_1 receptors is thus critical for correct interpretation of an incoming signal.

In prefrontal cortex, α_{2A} and D_1 receptors are often located on the spines of cortical pyramidal neurons, and can thus gate incoming signals (Figures 12-14 through 12-18). Alpha-2A receptors are linked to the molecule cyclic adenosine monophosphate (cAMP) via the inhibitory G protein, or Gi (Figure 12-14). D_1 receptors, on the other hand, are linked to the cAMP signaling system via the stimulatory G protein (Gs) (Figure 12-14). 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 α_{2A} receptor, the activated Gi-linked system inhibits cAMP, thereby closing the HCN channel (Figure 12-15). Closure of the channel allows the signal to go through the spine and down the neuron, thereby strengthening network connectivity with similar neurons (Figure 12-15). So in general, in the prefrontal cortex, stimulation of α_{2A} receptors strengthens an incoming signal.

By contrast, stimulation of D_1 receptors leads to weakening of the signal (Figure 12-16). That is, when DA, or a DA agonist, binds to a D_1 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 D_1 receptors will, in contrast to stimulation of α_{2A} receptors, result in the dissipation and/or weakening of a signal. The mechanism of action of α_{2A} (Figure 12-15) and D_1 receptors (Figure 12-16) explains in general why moderate stimulation of both types of receptors

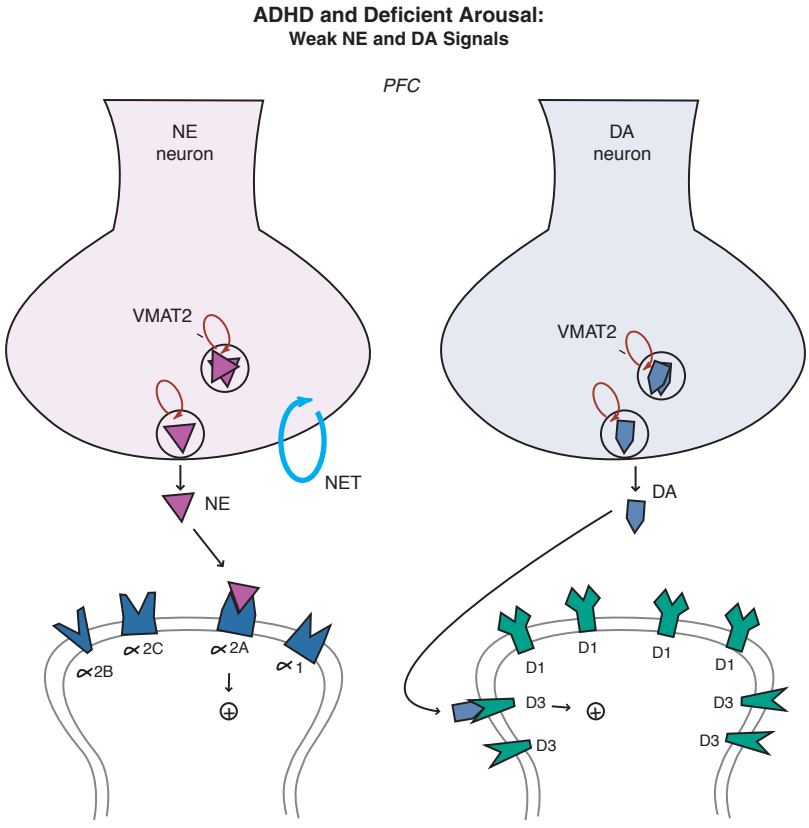

Figure 12-11. ADHD and deficient arousal. Besides being a key player in the arousal pathways, the prefrontal cortex is also the main brain area where imbalances in NE and DA systems hypothetically occur in ADHD. Deficient signaling in prefrontal cortical DA and NE pathways is reflected by reduced stimulation of postsynaptic receptors. Agents that can lead to (1) increased release of these two neurotransmitters, or (2) increased tonic firing of these neurons, will be hypothetically beneficial in patients with ADHD by bringing prefrontal activity back to optimal level.

(Figure 12-14) is preferred in order to strengthen the signal-to-noise ratio in prefrontal cortical neurons (Figure 12-17).

What happens following concurrent stimulation of α_{2A} and D_1 receptors by NE and DA, respectively (Figure 12-17)? While the exact localization and density of α_{2A} and D_1 receptors within various cortical areas are still 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," then D_1 receptor stimulation can reduce the noise and α_{2A} receptor stimulation can increase the signal to result in proper prefrontal cortex functioning (Figure 12-17). Theoretically, this will result in adequate guided attention (Figure 12-13), 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 D_1 and α_{2A} receptors on the spines of these pyramidal neurons (Figure 12-18)? Deficient DA and NE input will theoretically lead to increased noise and decreased signal, respectively, thus preventing a coherent signal from being sent (Figure 12-18). Hypothetically, this could cause hyperactivity, inattention, impulsivity, or some combination of symptoms, depending upon the localization of the mis-tuned pyramidal neuron in prefrontal cortex (Figures 12-3 through 12-8). 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 with which a patient is ailing. With this in mind, Figures 12-7 and 12-8 show how pyramidal neurons in different brain areas may be responsible for the different symptom presentations in ADHD.

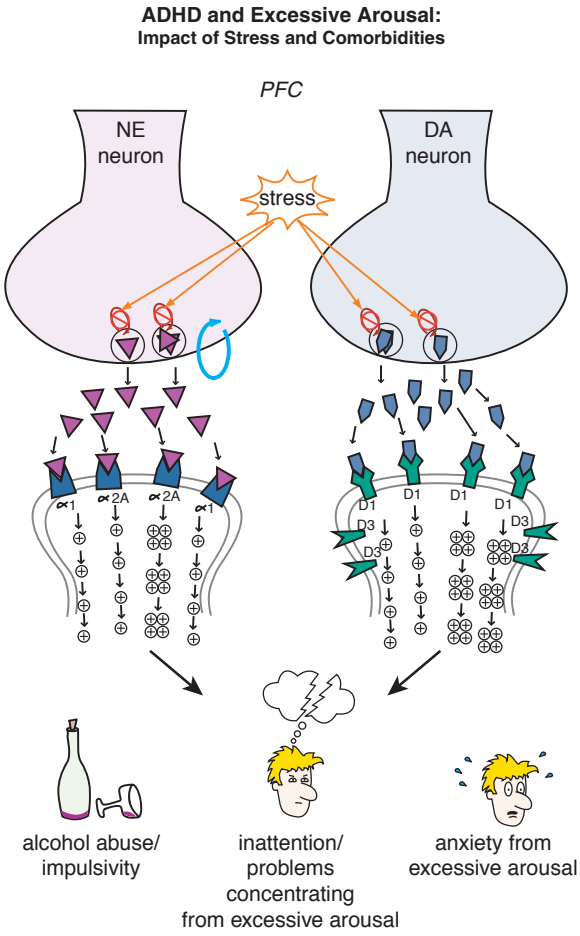

Figure 12-12. ADHD and excessive arousal. Nontreated adults with ADHD can often be stressed as they are trying to deal with their disorder while at the same time attempting to accomplish as much as their peers. Unfortunately, stress can activate NE and DA circuits in the prefrontal cortex, leading to an excess of phasic NE and DA firing. This excessive NE and DA neurotransmission may herald the development of impulsivity, inattention, and comorbidities associated with ADHD such as anxiety and substance abuse. This emphasizes the notion that treatment of all comorbid disorders is necessary to attain good patient outcomes.

Neurodevelopment and ADHD

ADHD has traditionally been considered a childhood disorder, but this perspective is rapidly changing, with ADHD now being seen also as a major psychiatric disorder of adults, with some major differentiating features between ADHD in children and adolescents (Table 12-1). Nevertheless, the classic form of ADHD has onset by age seven, possibly related to abnormalities in prefrontal cortex circuits that begin before age seven but last a lifetime (Figure 12-19). Synapses rapidly increase in prefrontal cortex by age six, and then up to half of them are rapidly eliminated by adolescence (Figure 12-19). The timing of onset of ADHD suggests that the formation of synapses, and perhaps more importantly the selection of synapses for removal in prefrontal cortex during childhood, may contribute to the onset and lifelong pathophysiology of this condition (Figure 12-19). Those who are able to compensate for these prefrontal abnormalities by new synapse formation may be the ones who "grow out of their ADHD," and this may explain 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 12-2 through 12-8). In fact, genes that code for subtle molecular abnormalities are thought to be just as important to the etiology of ADHD as they are to the etiology of schizophrenia. 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. The genetic factors linked to schizophrenia are discussed extensively in Chapter 4. The major genes implicated in ADHD are those linked to the neurotransmitter dopamine, although links to the genes for the α_{2A}-adrenergic receptor, serotonin receptors, and some other proteins are also under intense investigation. Environmental factors inevitably contribute to ADHD, as they do to so many other psychiatric disorders. This includes factors such as preterm birth, maternal smoking during pregnancy, and others.

The impact of neurodevelopment on the specific symptom patterns of ADHD is shown in Figure 12-20. Inattentive symptoms are not really seen 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 six. Once inattention becomes a prominent symptom of ADHD, it remains so over the life cycle (Figure 12-20). However, hyperactivity declines notably by adolescence and early adulthood, while recognized comorbidities

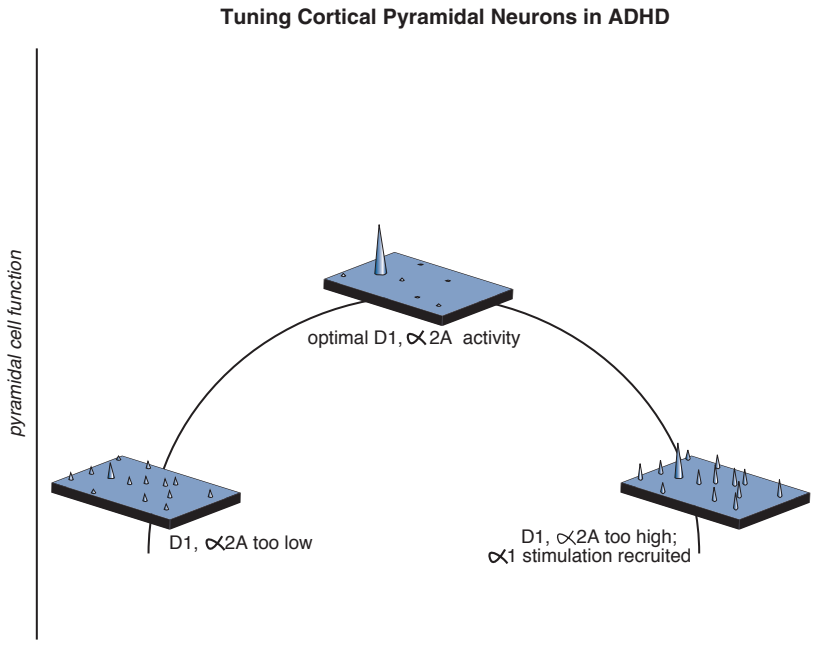

Figure 12-13. ADHD and maladaptive signal-to-noise ratios. In order for the prefrontal cortex to work properly, moderate stimulation of α_2 receptors by NE and D_1 receptors by DA is required. In theory, the role of NE is to *increase* the incoming *signal* by allowing for increased connectivity of the 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 α_{2A} and D_1 receptors is moderate and pyramidal cell function is optimal. If stimulation at α_{2A} and D_1 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.

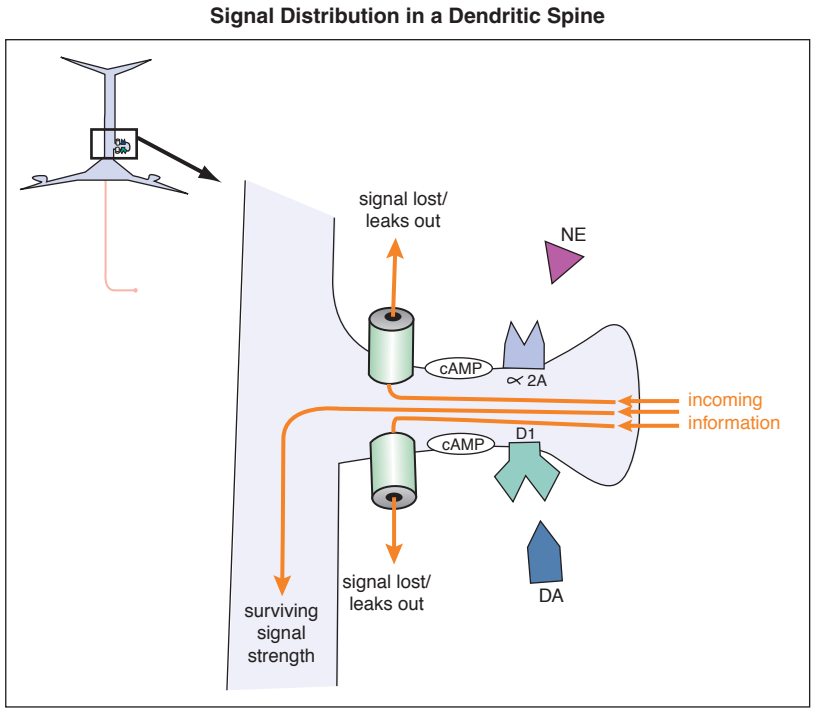

Figure 12-14. Signal distribution in a dendritic spine. The location of α_{2A} and D_1 receptors on dendritic spines of cortical pyramidal neurons in the prefrontal cortex allows them to gate incoming signals. Both α_{2A} and D_1 receptors are linked to the molecule cyclic adenosine monophosphate (cAMP). The effects on cAMP from NE and 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.

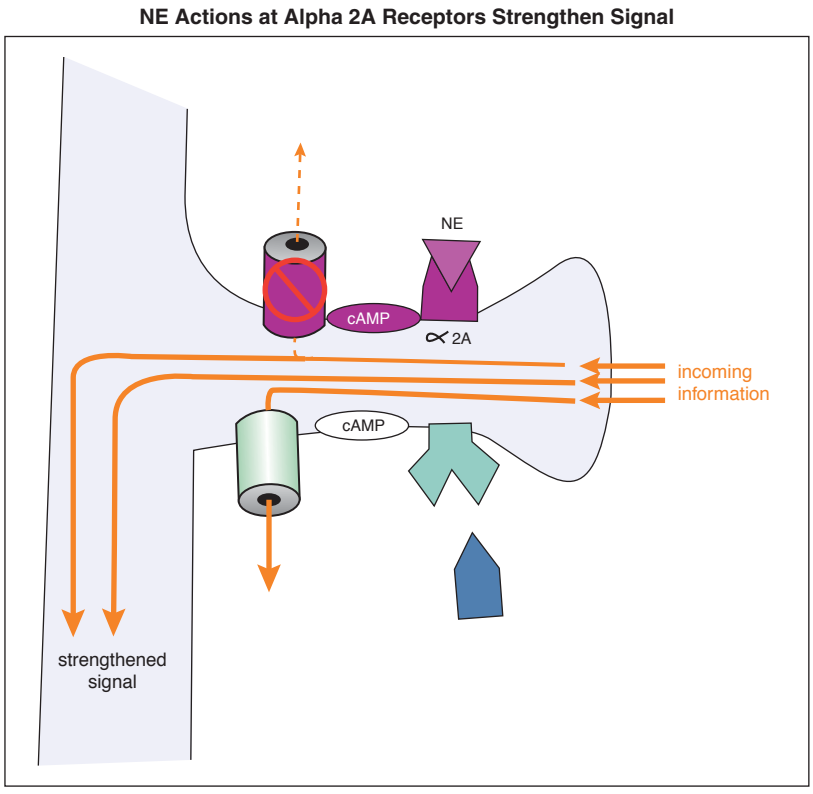

Figure 12-15. Norepinephrine actions at α_{2A} receptors strengthen the incoming signal. Alpha$_{2A}$ receptors are linked to cAMP via an inhibitory G protein (Gi). When NE occupies these α_{2A} receptors, the activated Gi-linked system inhibits cAMP and the HCN channel is closed, preventing loss of the incoming signal.

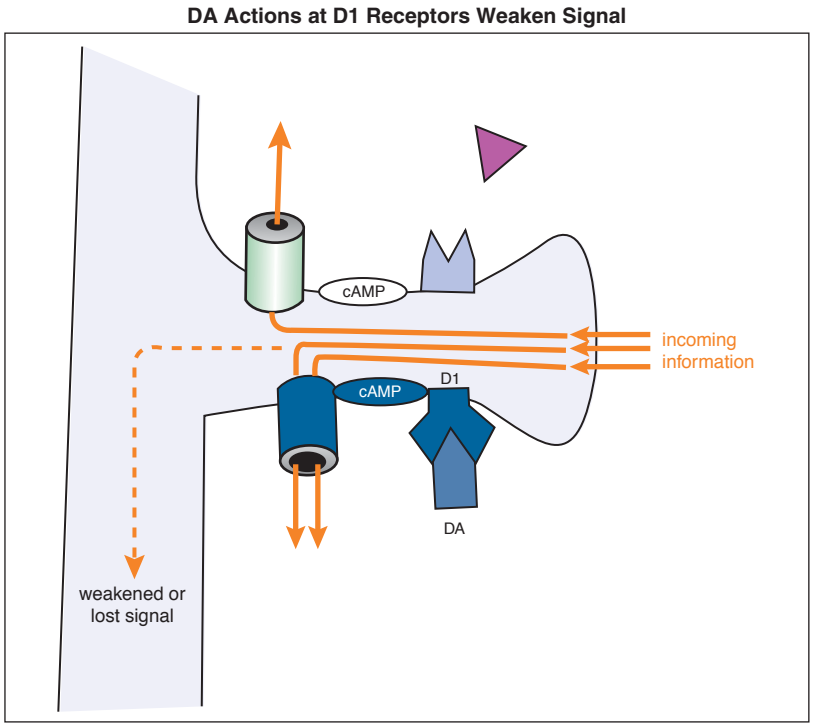

Figure 12-16. Dopamine actions at D_1 receptors weaken the incoming signal. D1 receptors are linked to cAMP via a stimulatory G protein (Gs). When DA occupies these D_1 receptors, the activated Gs-linked system activates cAMP, leading to opening of HCN channels. The opening of the HCN channels, especially if excessive, will lead to loss of the incoming signal before it can be passed along.

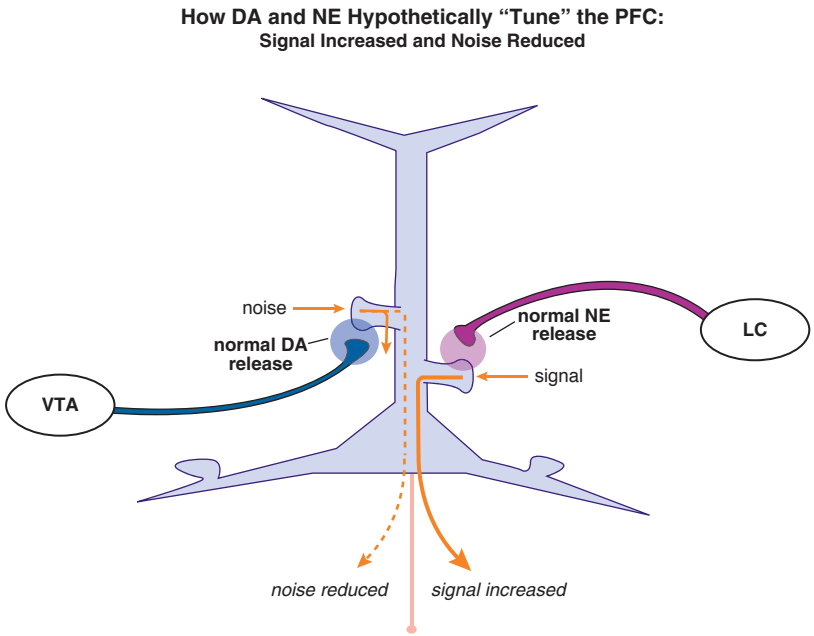

Figure 12-17. Dopamine and norepinephrine "tune" the PFC. The same pyramidal neuron may receive NE input from the locus coeruleus (LC) on one spine and DA input from the ventral tegmental area (VTA) on another spine. When properly "tuned," D_1 receptor stimulation will reduce the noise while α_{2A} receptor stimulation will increase the signal, resulting in appropriate prefrontal cortex functioning, guided attention, focus on a specific task, and control of emotions and impulses.

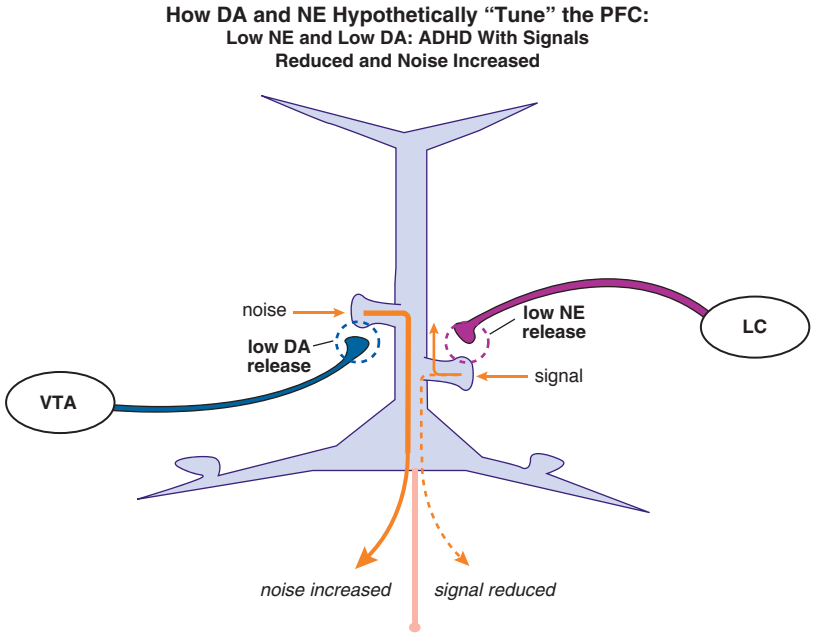

Figure 12-18. Dopamine and norepinephrine improperly "tune" the PFC in ADHD. Deficient DA will theoretically lead to increased noise, whereas deficient NE input will cause a decrease in the incoming signal. Hypothetically, this improper tuning of the PFC by DA and NE can lead to hyperactivity, or inattention, or both. Depending on the relative levels of both DA and NE, a person could display a wide range of clinical symptoms.

skyrocket in frequency as ADHD patients enter adulthood (Figure 12-20).

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 (Table 12-1). The reasons for this are multiple, starting with the diagnostic requirement that ADHD symptoms must begin by age seven. Adults often have difficulty making accurate retrospective diagnoses, especially if the

Table 12-1 Differences in ADHD in adults versus children and adolescents

Children 6–12 / Adolescents 13–17	Adults > 18
7–8% prevalence	4–5% prevalence
Easy to diagnose	Hard to diagnose • Inaccurate retrospective recall of onset • Onset by age 7 too stringent • Late onset, same genetics, comorbidity, and impairment
Diagnosed by pediatricians, child psychiatrists, child psychologists	Diagnosed by adult psychiatrists, adult mental/medical health professionals
High levels of identification and treatment: > 50% treated	Low levels of identification and treatment: < 20% treated
Stimulants prescribed first- and second-line	Nonstimulants often prescribed first-line
2/3 of stimulant use is under age 18, most of this under age 13	1/3 of stimulant use is age 18 or over
1/3 of atomoxetine use is under age 18, most of this over age 12	2/3 of atomoxetine use is age 18 or over

condition was not identified 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 seven, so-called late-onset ADHD. Many cases have onset up to the age of 12 and some up to the age of 45. Do these patients have ADHD? Genetic studies suggest that full syndrome ADHD with onset after age seven has similar psychiatric comorbidity, functional impairment, and familial transmission to ADHD with onset by age seven. Thus, there is a movement to consider the age of onset in some diagnostic criterion as too stringent for the diagnosis of ADHD in adults.

Differences in diagnostic rates in children versus adults may also be due to differences in referral patterns and in the specialties of practitioners who treat children versus those who treat adults. Most children with ADHD are diagnosed and treated by pediatricians, child psychiatrists, and child psychologists and are referred by parents and teachers with a high degree of suspicion for the diagnosis, generally requesting a trial of a stimulant, and usually these are patients without comorbidity. On the other hand, most adults with ADHD are self-referred and seen by psychiatrists and adult mental and medical health professionals; adult cases mostly have a comorbid condition that is the focus of treatment, not their ADHD. Thus, adult practitioners may prioritize the treatment of these other conditions over ADHD (see Figure 12-21) to the extent that ADHD is never formally diagnosed, nor is it specifically targeted for treatment.

There are also many differences in how ADHD is treated in children and adolescents compared to adults (Table 12-1). For example two-thirds of all stimulant use for ADHD is in patients under the age of 18, most of these under the age of 13. Stimulant use falls off in adolescents and then falls way off in adults. Only one-third of all stimulant use for ADHD is in adults. On the other hand, two-thirds of all atomoxetine use is in adults, one-third in those under the age of 18, mostly in adolescents (Table 12-1). Why these differences? One reason could be that many adult practitioners do not like to prescribe controlled substances such as stimulants. Another reason could be due to the differences in the rates of comorbidity of children versus adults with ADHD, and in the types of comorbid conditions of children versus adults with ADHD. Thus, the frequent comorbidities of substance abuse, anxiety disorders, and bipolar or mixed states can limit the utility and tolerability of stimulants in the typical adult ADHD patient with these comorbidities. Augmenting antidepressants and anxiolytics with nonstimulants can therefore be preferable. There is also much more off-label use of the NDRI antidepressant bupropion, the various SNRIs, and the wake-promoting agents modafinil and armodafinil in adults than in children, often as augmenting agents in comorbid adult ADHD.

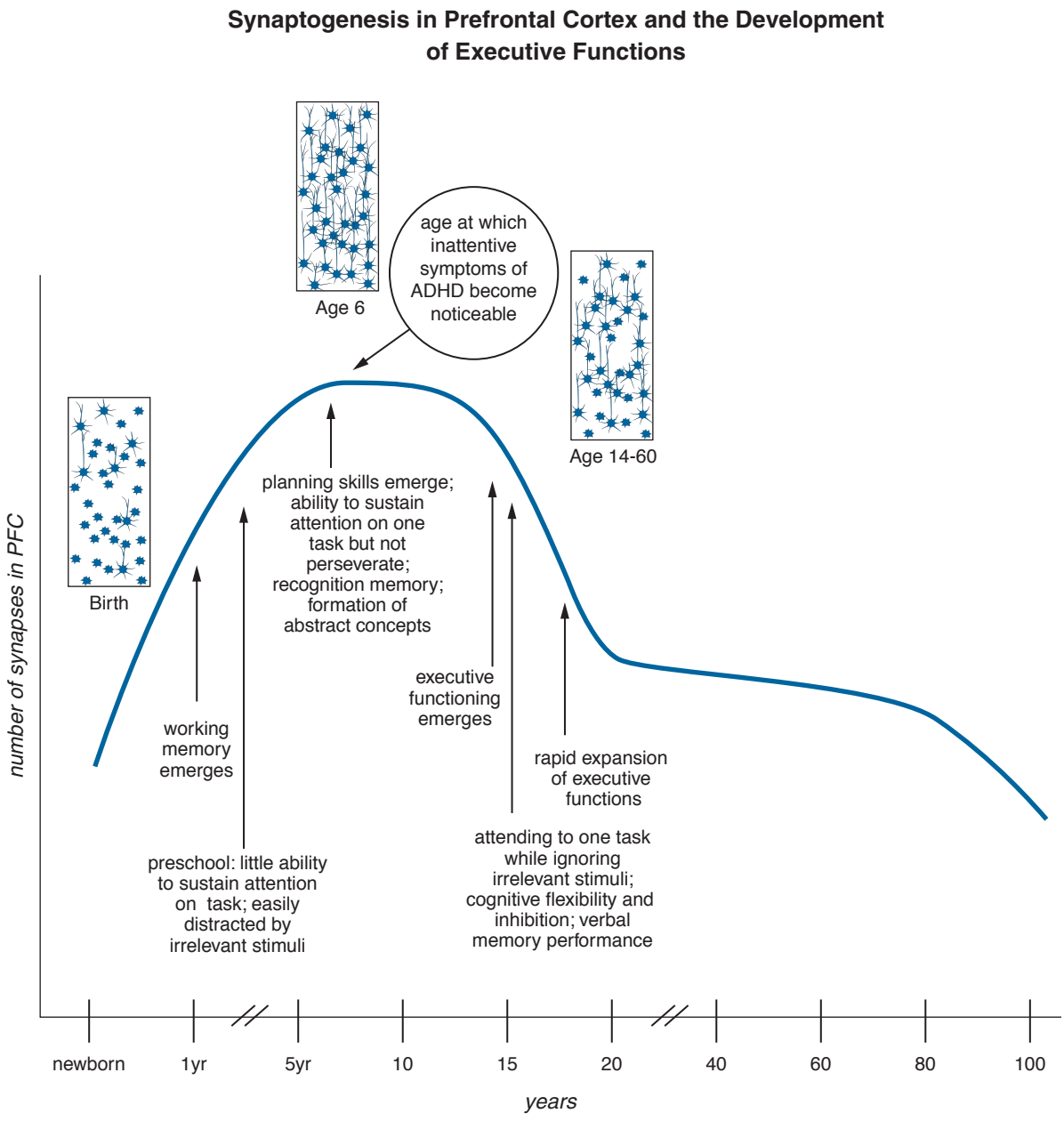

Figure 12-19. Synaptogenesis in the PFC and the development of executive functions. Synaptogenesis in the prefrontal cortex might be responsible for altered connections that could prime the brain for ADHD. Specifically, executive function develops throughout adolescence. At one year of age, working memory emerges. Around three to four 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 six to seven, 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 six.

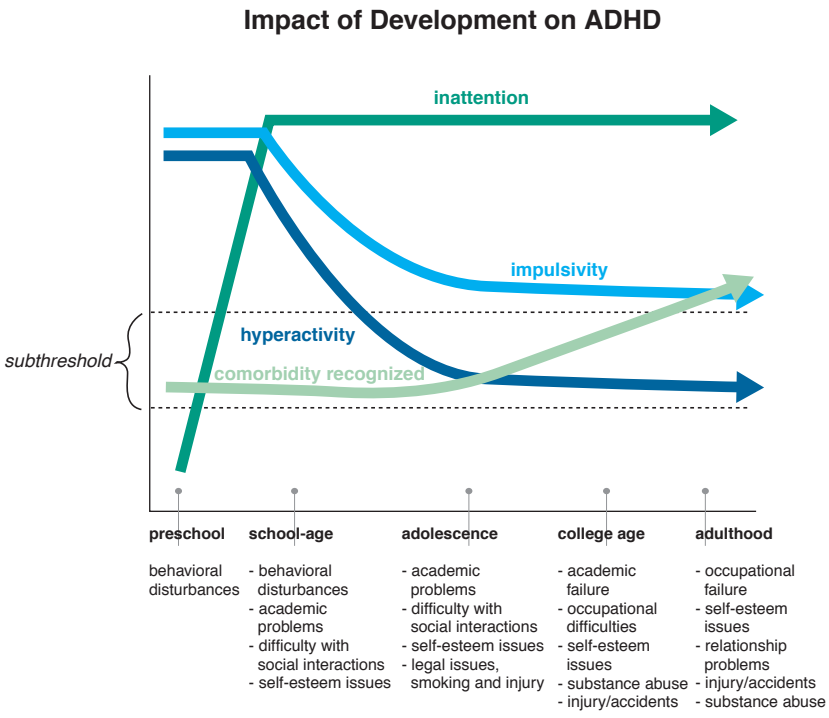

Figure 12-20. Impact of development on ADHD. The evolution of symptoms across the ages shows that although hyperactivity and impulsivity are key symptoms in childhood, inattention becomes prevalent as the patient ages. Additionally, the rates of recognized comorbidities increase over time. This could be due to the fact that the comorbidities were overlooked in children with ADHD, or because ADHD was never diagnosed in some patients presenting with anxiety or learning disabilities. One could say that "the jury is still out" on this issue.

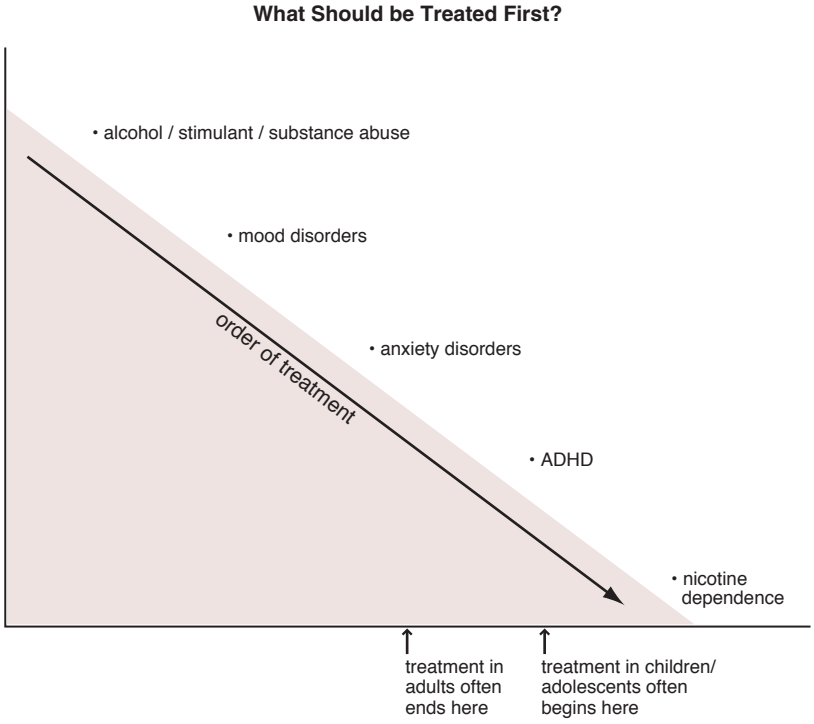

Figure 12-21. ADHD and comorbidities: what should be treated first? What should a psychopharmacologist do with a patient with ADHD and comorbid disorders? Once the proper diagnosis has been reached, it is imperative to treat all disorders appropriately, and in terms of highest degree of impairment. This 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 therefore be established for each patient, depending on his/her symptomatic portfolio.

Currently, the recognition and treatment of ADHD in adults, tailoring the diagnostic and psychopharmacologic considerations to the unique features of this illness in adults, is increasing at a rapid pace. Thus, there is a call for more recognition that ADHD is only half the problem in mostly comorbid adults, and that treatment of ADHD in adults generally means concomitant treatment of ADHD with one or more additional disorders, and generally with a combination of drugs for the different conditions. It is increasingly recognized that atomoxetine (or another NET inhibitor) augmentation of antidepressants and anxiolytics can not only improve cognitive symptoms of ADHD, but has the potential of improving anxiety symptoms, depressive symptoms, and perhaps even heavy drinking. It is possible that the α_{2A} selective adrenergic agonist guanfacine ER, approved for use in children, may also be useful for off-label treatment of adults. Long-acting stimulants may also be useful in adults, not just those stimulants specifically approved in adults, but also those newer agents first tested and approved for use in children which can be used for off-label treatment of adults.

Treatment

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 while other symptoms are targeted for improvement first (Figure 12-21). Although there are no definitive studies on this approach, clinical experience from many experts suggests that in such 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 be managed top line (Figure 12-21). Treating ADHD may also have to await improvement from mood and anxiety disorder treatments, with ADHD seen as more of a fine-tune adjustment to a patient's symptom portfolio (Figure 12-21).

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 perhaps in isolation, without necessarily evaluating possible comorbidities until they fail to respond robustly to stimulant treatment (Figure 12-21). In adults it can be so difficult to treat substance abuse, mood disorders, and anxiety disorders that the focus of therapeutic attention never gets to ADHD or certainly to nicotine dependence. Once the mood or anxiety disorder is improving, treatment can plateau or stop. Too often the focus of psychopharmacological management is the mood or anxiety disorder to the exclusion of any comorbid ADHD (or nicotine dependence). That is, ADHD can be considered a mere afterthought to be addressed if cognitive symptoms do not remit once the primary focus of therapeutic attention, 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 and 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 for long-term management of ADHD to eventually address the treatment of nicotine dependence once the ADHD symptoms are under control (Figure 12-21). Adults with ADHD smoke as frequently as adults with schizophrenia, about twice the rate of the normal adult 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 DA 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 14 on drug abuse.

Stimulant treatment of ADHD

General principles

As discussed above, and as illustrated in Figures 12-11 and 12-13, when both DA and NE are too low the strength of output in the prefrontal cortex is also too low, thus leading to reduced signal and increased

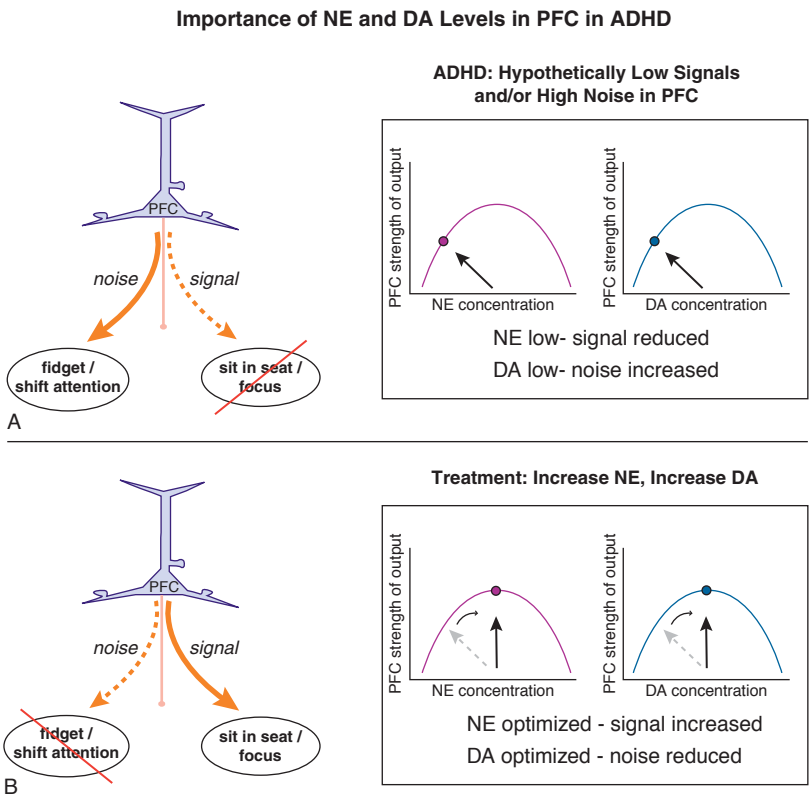

Figure 12-22. The importance of NE and DA levels in the PFC in ADHD. When both DA and NE are too low, i.e., on the left side of the inverted U-shaped curve, the strength of output in the prefrontal cortex is too low, leading to reduced signal and increased noise (A, right side). Inability to sit still and focus are often clinical manifestations of this imbalanced signal-to-noise ratio (A, left side). In order to treat these symptoms, it is necessary to increase strength output by dialing up (B, right side, toward the right on the U-shaped curve) the concentrations of both DA and NE until they reach the optimal dose (top of the inverted U-shaped curve).

noise (Figure 12-22A). Behaviorally, this could translate into a person not being able to sit in his/her seat and focus, and fidgeting and shifting attention (Figure 12-22A). 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 12-22B). This can be done both by 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 (Figure 12-13). The theory is that at first 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 in high NE and DA release, yet causing reduced signals and inefficient information processing (Figure 12-23A). 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 12-23B). Ultimately the appropriate treatment is to increase NE and DA concentrations to allow for normalization of behavior (Figure 12-23C: noise is reduced and signal is increased).

Experienced clinicians are well aware that such patients with too much DA and NE (represented in Figure 12-23A), too little DA and NE (represented in Figure 12-23B), or a combination of these in different pathways, can be very difficult to treat. For example, in children, the combination of tics generally representing excessive DA activation in striatum may require DA-blocking antipsychotics, and it can be very difficult to treat simultaneously in patients with ADHD who have deficient DA activation in cortex and require DA-enhancing stimulants. Stimulants may help the ADHD symptoms but make the tics much worse. Children and adolescents who have conduct disorder, oppositional disorders, psychotic

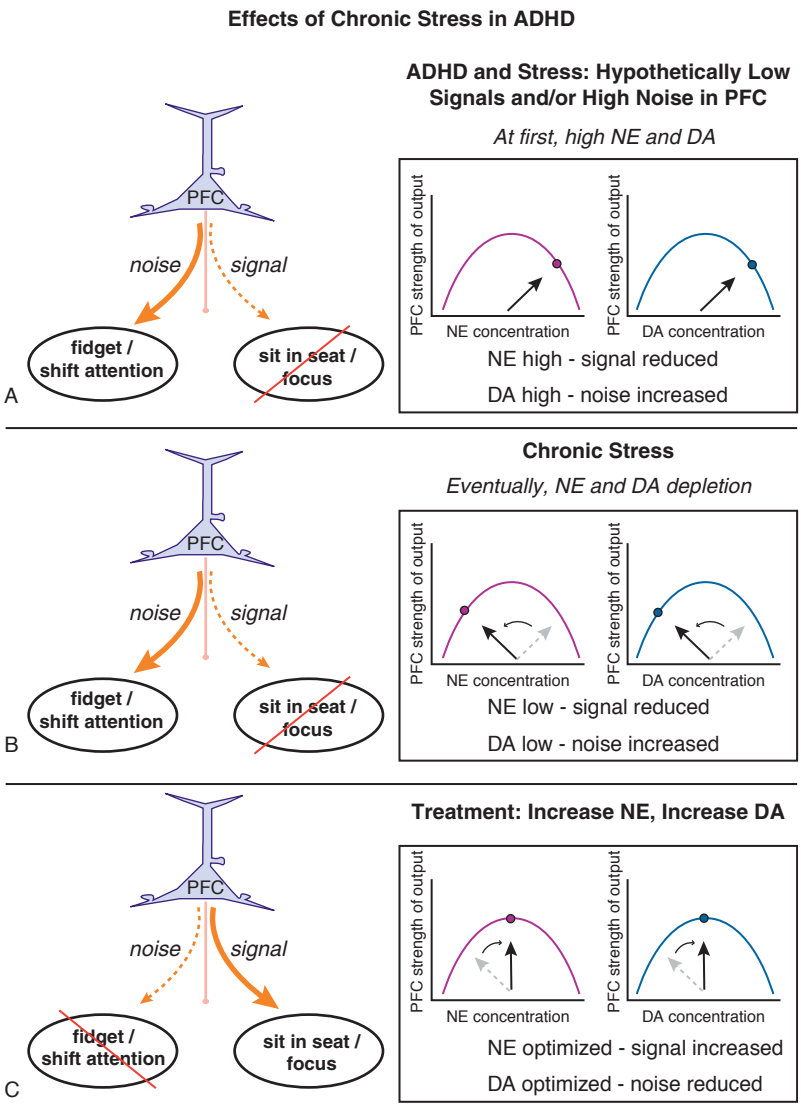

Figure 12-23. Chronic stress in ADHD. Excessive activation of NE and DA in prefrontal cortex (PFC) can lead to ADHD by increasing the noise and decreasing the signal. At first, the added stress of suffering from the disorder can further dial up the noise and reduce the signal (A: high NE and DA concentration leading to decreased output). As chronic stress sets in, NE and DA levels plummet (B: low NE and DA concentration also leading to decreased output), but with no relief in terms of signal output. Treatments that increase NE and DA concentrations may normalize behavior (C: noise is reduced and signal is increased).

disorders, and/or bipolar mania or mixed conditions (theoretically associated with excessive DA activation in some prefrontal circuits: Figure 12-8) comorbid with ADHD (theoretically associated with deficient DA activation in other prefrontal circuits: Figure 12-7) are among the most challenging patients for clinicians treating young patients.

Conditions of excessive DA activation suggest treatment with an atypical antipsychotic, yet ADHD suggests treatment with a stimulant. Can these two agents be combined? In fact, in heroic cases stimulants can be combined with atypical antipsychotics. The rationale for this combination exploits the fact that atypical antipychotics simultaneously release DA in prefrontal cortex to stimulate D_1 receptors there while acting in limbic areas to block D_2 receptors there. This mechanism of action of atypical antipsychotics is discussed extensively in Chapter 5. In patients who may require atypical antipsychotic treatment for psychotic or manic symptoms, yet still have ADHD, it is sometimes possible to augment the atypical antipsychotic cautiously with a stimulant, thereby increasing DA release to an even greater extent to act at D_1 receptors in prefrontal cortex, hopefully reducing ADHD symptoms while blocking DA stimulation at D_2 receptors sufficiently in limbic areas to

prevent worsening of mania or psychosis. Such an approach is controversial and best left to experts for difficult patients who fail to improve adequately on monotherapies.

For adults with ADHD and anxiety, it can be difficult or even self-defeating to try to treat anxiety with SSRIs/SNRIs or benzodiazepines while simultaneously administering a stimulant to improve the ADHD, only to cause the anxiety to worsen. For adults with ADHD and substance abuse, it makes little sense to give stimulants to drug abusers in 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 long-lasting NET inhibitor (norepinephrine reuptake inhibitors, NRIs), or an α_{2A}-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. Further controlled trials are needed to clarify the responsiveness of both ADHD and comorbid conditions to treatment with NET inhibitors or α_{2A}-adrenergic agonists.

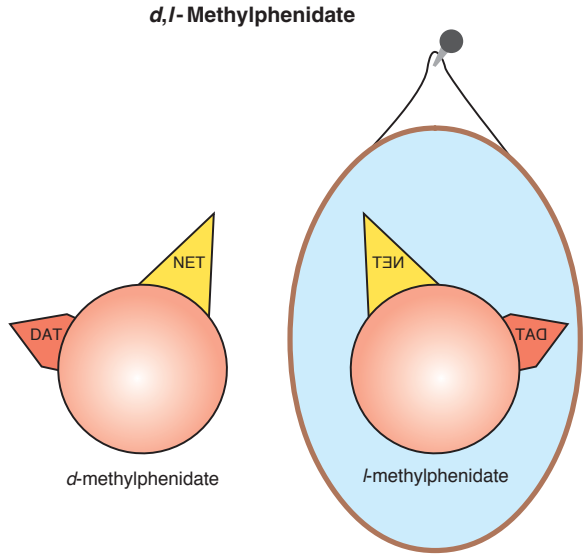

Figure 12-24. *d,l*-Methylphenidate. The racemic form of methylphenidate includes both the *d*- and the *l*-isomers. *d,l*-Methylphenidate will lead to increased release of DA in the nucleus accumbens and NE and DA in the prefrontal cortex by blocking the reuptake pumps, DAT and NET. The same effects are caused by *d*-methylphenidate. Methylphenidate comes in many different formulations, such as regular and chewable immediate-release tablets, new and old sustained-release tablets, new sustained-release capsules, and oral solutions, as well as a transdermal patch. The transdermal formulation may not only confer lower abuse potential but may also enhance adherence.

Methylphenidate

The mechanism of action of the stimulants is shown in Figures 12-24 through 12-31. Oral administration of clinically approved doses of the stimulant methylphenidate blocks the transporters for both NE and DA (NET and DAT) (Figures 12-25, 12-30, 12-31). Normally, dopamine is released (arrow 1 in Figure 12-25A), and then taken back up into the dopaminergic neuron by DAT (arrows 2 in Figure 12-25A), and finally stored in the synaptic vesicle by VMAT (arrows 3 in Figure 12-25A). Methylphenidate blocks DAT and NET allosterically, stopping the reuptake of dopamine via DAT (Figure 12-25B) and norepinephrine via NET (Figure 12-25C), with no actions on VMAT (Figures 12-25B and 12-25C). Methylphenidate blocks NET and DAT in much the same way as antidepressants block them (see discussion in Chapter 7 and Figure 7-36), namely by binding to NET and DAT at sites *distinct* from where monoamines bind NET and DAT, i.e., allosterically. Thus, methylphenidate stops the reuptake pumps so that no methylphenidate is transported into the presynaptic neuron (Figures 12-25B and 12-25C). Methylphenidate has a *d*- and an *l*-isomer (Figure 12-24), with the *d*-isomer being much more potent than the *l*-isomer on both NET and DAT binding (Figure 12-30). Methylphenidate is available as the single enantiomer *d*-methylphenidate in both immediate-release and controlled-release preparations.

Amphetamine

Oral administration of clinically approved doses of the stimulant amphetamine, like methylphenidate, also blocks the transporters both for NE and DA (NET and DAT), but in a different manner (Figures 12-26, 12-27, 12-28, 12-30, 12-31). Unlike methylphenidate and antidepressants, amphetamine is a competitive inhibitor and pseudosubstrate for NET and DAT (Figure 12-28), binding at the *same* site that the monoamines bind to the transporter, thus inhibiting NE and DA reuptake (Figure 12-28). At the doses of amphetamine used for the treatment of ADHD, the clinical differences in the actions of amphetamine versus methylphenidate can be relatively small. However, at the high doses of amphetamine used by stimulant addicts, additional pharmacologic actions of amphetamine are triggered. Following competitive

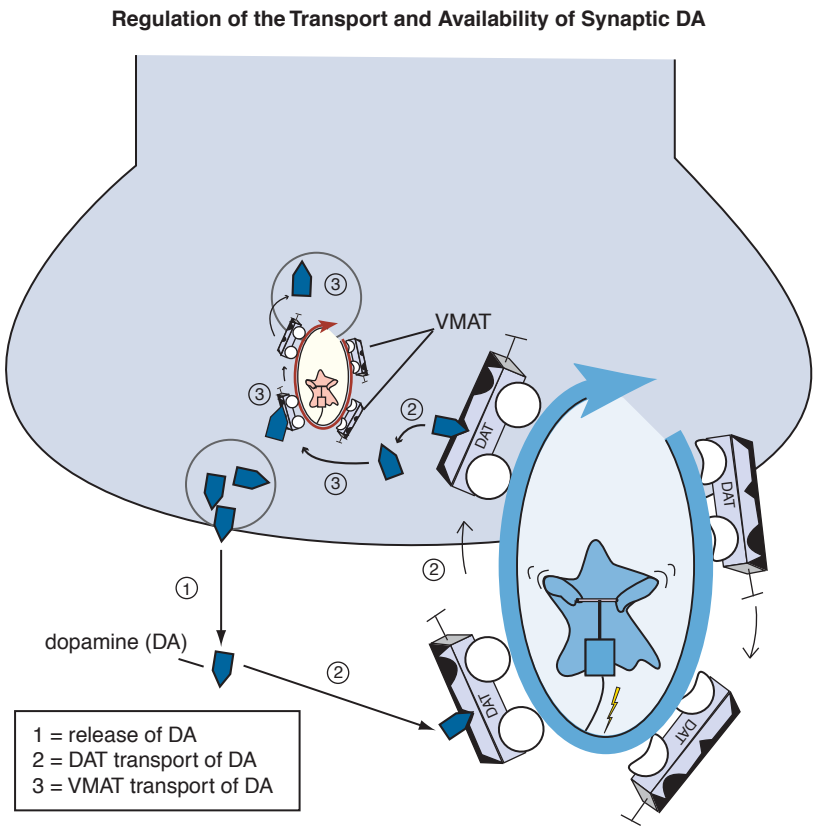

Figure 12-25A. Regulation of transport and availability of synaptic dopamine. To understand how stimulants work, it is necessary to know how DA is cleared from the synaptic cleft and stored. The regulation of synaptic DA is dependent upon proper functioning of two transporters, namely the dopamine transporter (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 DAT (2). Once inside the terminal, DA is "encapsulated" into vesicles via VMAT (3). These DA-filled 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, nor in the DA terminal. By "engulfing" DA into vesicles it is possible for the DA neuron to ensure the viability of DA.

inhibition of DAT (Figure 12-28A) amphetamine is actually transported as a hitchhiker into the presynaptic DA terminal, an action not shared by methylphenidate or antidepressants (Figure 12-28A). Once there in sufficient quantities, such as occurs with doses taken for abuse, amphetamine is also a competitive inhibitor of the vesicular transporter (VMAT2) for both DA and NE (Figure 12-28B). Once amphetamine hitchhikes another ride into synaptic vesicles, it displaces DA there, causing a flood of DA release (Figure 12-28C). As DA accumulates in the cytoplasm of the presynaptic neuron, it causes the DAT 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 12-28D). These pharmacologic actions of high-dose amphetamine are not linked to any therapeutic action in ADHD but to reinforcement, reward, euphoria, and continuing abuse. Actions of high-dose amphetamine, methamphetamine, and cocaine, given orally in immediate-release formulations or intranasally, intravenously, or smoked, are discussed further in Chapter 14 on drug abuse.

Amphetamine has a *d*- and an *l*-isomer (Figures 12-26, 12-27, 12-30). The *d*-isomer is more potent than the *l*-isomer for DAT binding, but *d*- and *l*-amphetamine isomers are more equally potent in their actions on NET binding. Thus, *d*-amphetamine preparations will have relatively more action on DAT than NET; mixed salts of both *d*- and *l*-amphetamine will have relatively more action on NET than *d*-amphetamine but overall still more action on DAT than NET (see Figure 12-30). These pharmacological mechanisms of action of the stimulants come into play particularly at lower therapeutic doses utilized for the treatment of ADHD. *d*-Amphetamine also comes in a formulation linked to the amino acid lysine (Figure 12-27) which is not absorbed until slowly cleaved into active *d*-amphetamine in the stomach, and slowly, rather than rapidly, absorbed.

Slow-release versus fast-release stimulants and the mysterious DAT

Rapid and high degrees of DAT occupancy by stimulants may cause euphoria and lead to abuse, whereas slow onset and lower degrees of DAT occupancy

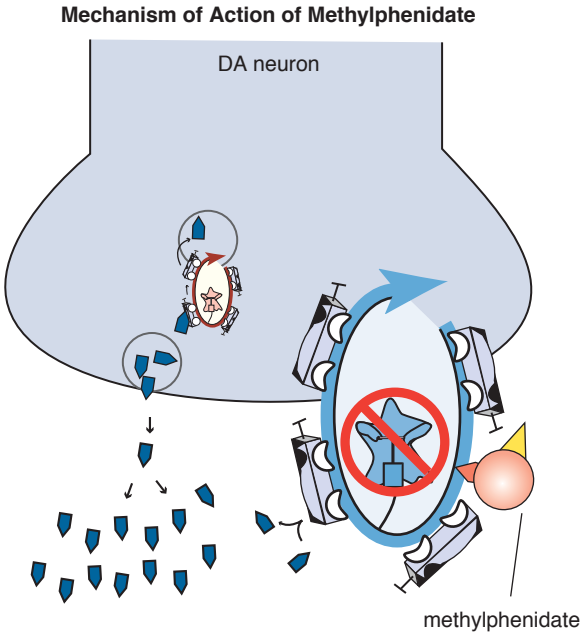

Figure 12-25B. Mechanism of action of methylphenidate: dopaminergic neurons. Methylphenidate works at DAT similar to how selective serotonin reuptake inhibitors (SSRIs) work at the serotonin transporter (SERT), namely by blocking the reuptake of DA into the terminal. Methylphenidate basically freezes the transporter in time, preventing DA reuptake and thus leading to increased synaptic availability of DA. Unlike amphetamine, methylphenidate is not itself taken up into the DA terminal via the transporter.

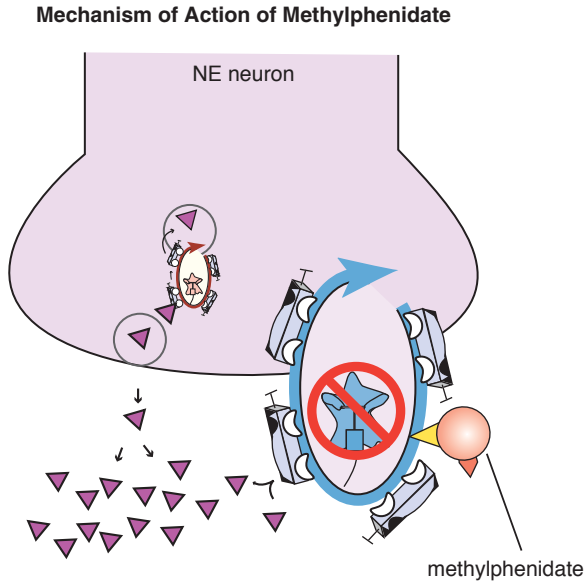

Figure 12-25C. Mechanism of action of methylphenidate: noradrenergic neurons. Methylphenidate works at NET in a manner similar to its actions at DAT, namely by blocking the reuptake of NE into the terminal. Methylphenidate freezes the transporter in time, preventing NE reuptake and thus leading to increased synaptic availability of NE. Unlike amphetamine, methylphenidate is not itself taken up into the NE terminal via the transporter.

may be consistent with antidepressant actions and improvement in attention in ADHD. The DAT appears therefore to be a somewhat mysterious target for drugs, giving one set of responses if occupancy by a given stimulant is rapid, saturating, and short-acting (namely, resulting in "highs" and reinforcement and eventually compulsive use) (Figure 12-30), and a completely different set of responses if occupancy by that same stimulant of that very same DAT target ramps up slowly, has incomplete target saturation, and lasts a long time (resulting in therapeutic actions in ADHD and depression without "highs" or abuse) (Figure 12-31). Thus, pharmacokinetic considerations seem to be just as important to the actions of stimulants in general, and in ADHD in particular, as their pharmacodynamic mechanisms.

Clinicians, parents, and patients often ask if there is a difference between the use of stimulants in the treatment of ADHD and the abuse of stimulants in substance-use disorders. The difference lies less in the mechanism of action, but more in the nature of the mysterious DAT, which has very different clinical responses to different routes of administration and doses, and thus how quickly, how strongly, and how completely DAT is blocked. When using stimulants to treat a patient it may be preferable to obtain a slow-rising, constant, steady-state level of the drug (Figure 12-29A). Under those circumstances the firing pattern of DA will be 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 12-10). However, as seen in Figure 12-13, DA stimulation follows an inverted U-shaped curve, such that too much DA will mimic the actions of DA in stress (Figure 12-12) at higher doses, or mimic drug abuse at the highest doses (Figure 12-29B). Thus a pulsatile drug administration that causes intermittent release of DA, unlike constant release, will lead to the highly reinforcing pleasurable effects of drugs of abuse.

The past several years have seen a flurry of new drug development activities aimed at optimizing the drug delivery characteristics of stimulants for ADHD. These are not mere patent extension gimmicks, nor

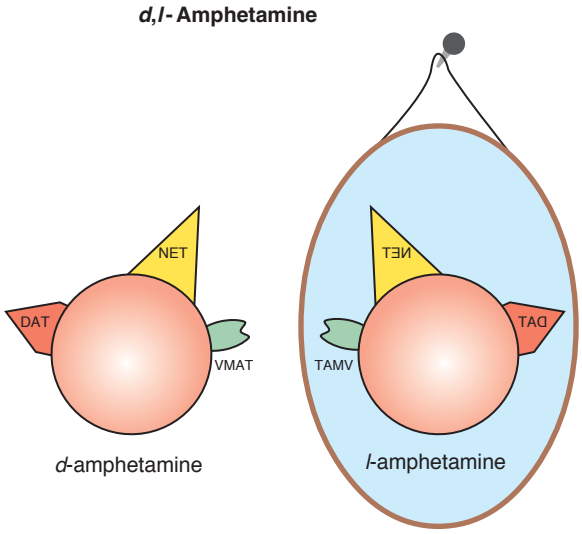

Figure 12-26. *d,l*-Amphetamine. *d,l*-Amphetamine includes both *d*- and *l*-enantiomers. Similar to *d*-amphetamine, *d,l*-amphetamine is a competitive inhibitor of DAT, NET, and VMAT. There are, however, subtle differences. For example the *d*-isomer is more potent for DAT binding, and both *d*- and *l*-isomers are equipotent for NET binding. This translates to the following actions of these compounds: *d*-amphetamine will have relatively more action on DAT than NET, while the mixed salts of both *d*- and *l*-amphetamine will have relatively more action on NET than the *d*-isomer, but overall still more action on DAT than NET. These small differences are especially noticeable at the lower doses of both *d*-amphetamine and *d,l*-amphetamine and in some individual patients. Different formulations of *d,l*-amphetamine are approved for the treatment of ADHD in children and adults.

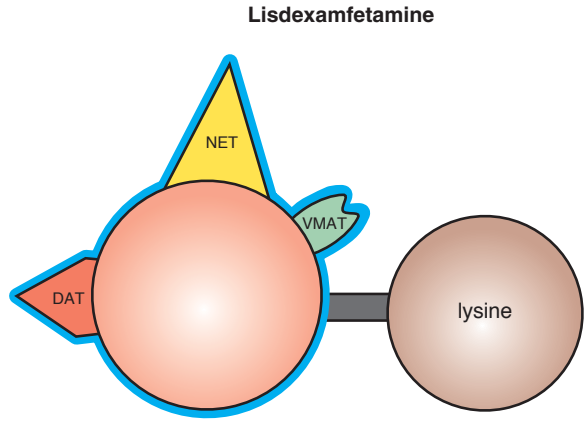

Figure 12-27. Lisdexamfetamine. Lisdexamfetamine is the prodrug of *d*-amphetamine, linked to the amino acid lysine. It is only centrally active as *d*-amphetamine once it has been cleaved in the stomach into the active compounds *d*-amphetamine plus free L-lysine.

mere convenience features, although it is certainly an advantage for a child not to have to take a second dose of a stimulant in the middle of the day at school. More importantly, the "slow-dose" stimulants, shown in Figure 12-30, optimize the rate, the amount, and the length of time that a stimulant occupies NET and DAT for therapeutic use in ADHD. Optimization for ADHD means occupying enough of the NET in prefrontal cortex at a slow enough onset and long enough duration of action to enhance tonic NE signaling there via α_{2A} receptors and to increase tonic DA signaling there via D_1 receptors, yet occupying little enough of the DAT in nucleus accumbens so as not to increase phasic signaling there via D_2 receptors (Figure 12-30). It appears that ADHD patients have their therapeutic improvement by stimulants at the mercy of how fast, how much, and for how long stimulants occupy NET and DAT. When this is done in an ideal manner with slow onset, robust but subsaturating drug levels, and long duration of action before declining and wearing off, the patient benefits with improved ADHD symptoms, hours of relief, and no euphoria (Figure 12-30). Tonic drug delivery of stimulants amplifies the desired tonic increases in DA and NE action for ADHD improvement for several hours. On the other hand, Figure 12-31 shows how *not* to treat ADHD with stimulants: namely by frequent high-dose and pulsatile delivery of short-acting stimulants, which approximates very closely the best way to use these agents for euphoria and reinforcement with amplifying phasic NE and DA signals (Figure 12-31).

Noradrenergic treatment of ADHD

Atomoxetine

Atomoxetine is a selective norepinephrine reuptake inhibitor or selective 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, since the prefrontal cortex lacks high concentrations of DAT, DA is inactivated in this part of the brain by NET. Thus, inhibiting NET increases both DA and NE in prefrontal cortex (Figures 12-32 and 12-33; see also discussion in Chapter 7 and Figure 7-34). 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 12-32). For this reason, in ADHD patients with weak NE and DA signals in prefrontal cortex, a selective NRI such as atomoxetine increases both NE and DA in

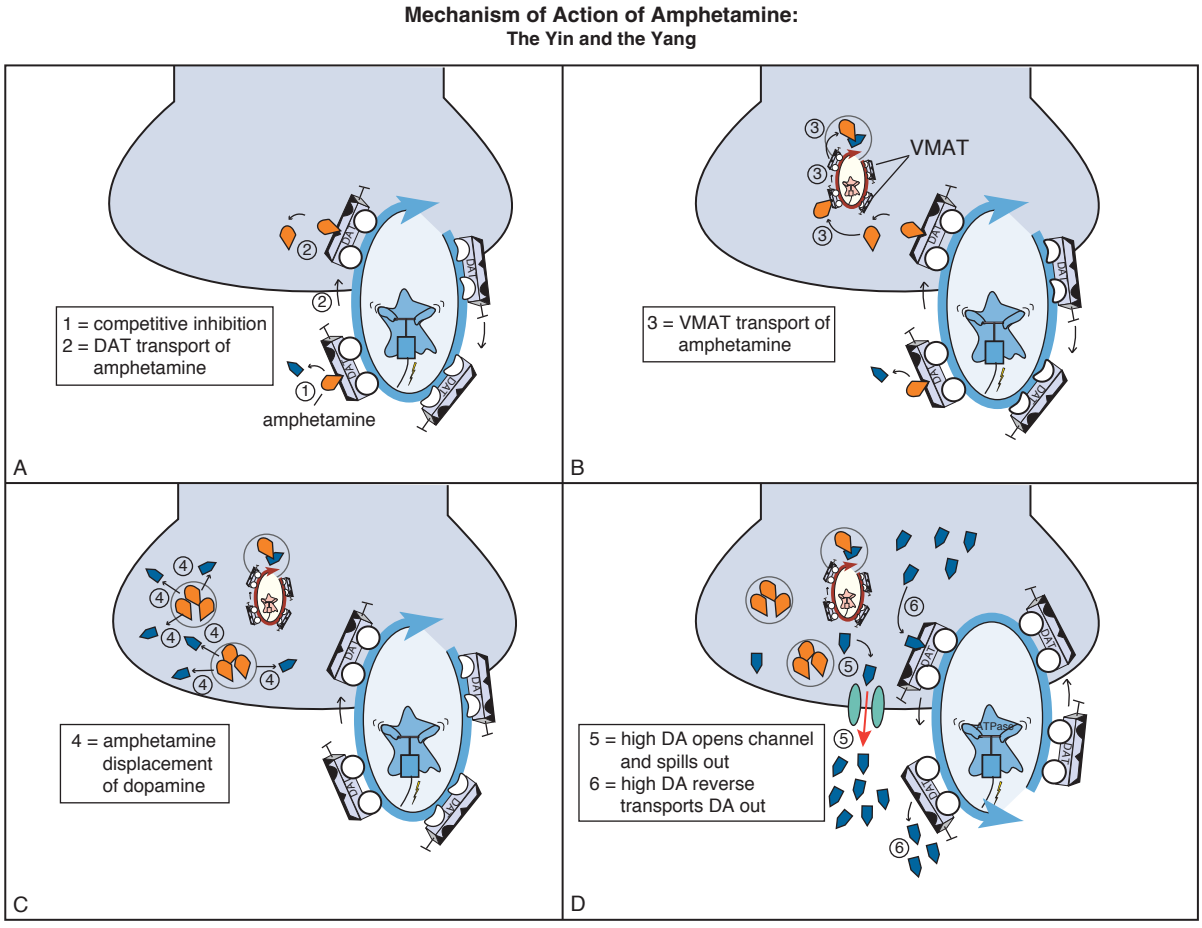

Figure 12-28. Mechanism of action of amphetamine: the yin and the yang. The yin – therapeutic and controlled drug delivery causes tonic-like increases; the yang – abusive doses and pulsatile drug delivery cause phasic-like increases. Shown here is amphetamine acting as a competitive inhibitor at DAT, thus competing with DA (1), or NE at NET (not shown). This is unlike methylphenidate's actions at DAT and NET, 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 DAT (2), where it can then also 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 DAT (6). This fast release of DA will lead to the euphoric effect experienced after amphetamine use.

prefrontal cortex, enhancing tonic signaling of both, but increases neither NE nor DA in accumbens. Therefore, atomoxetine has no abuse potential.

Atomoxetine is the only such agent approved for use in ADHD, but several other agents have NRI actions, including the approved (outside of the US) antidepressant and selective NRI reboxetine (Figure 7-38), and the various SNRIs, which not only have NRI actions but also serotonin reuptake inhibiting properties (Figures 7-30 through 7-34).

Bupropion is a weak NRI and also a weak DAT inhibitor known as a norepinephrine–dopamine reuptake inhibitor (NDRI). Figure 12-34 compares the actions of bupropion and atomoxetine (also discussed in Chapter 7: see Figures 7-35 through 7-37). Several tricyclic antidepressants 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 Figure 12-12 with the changes that

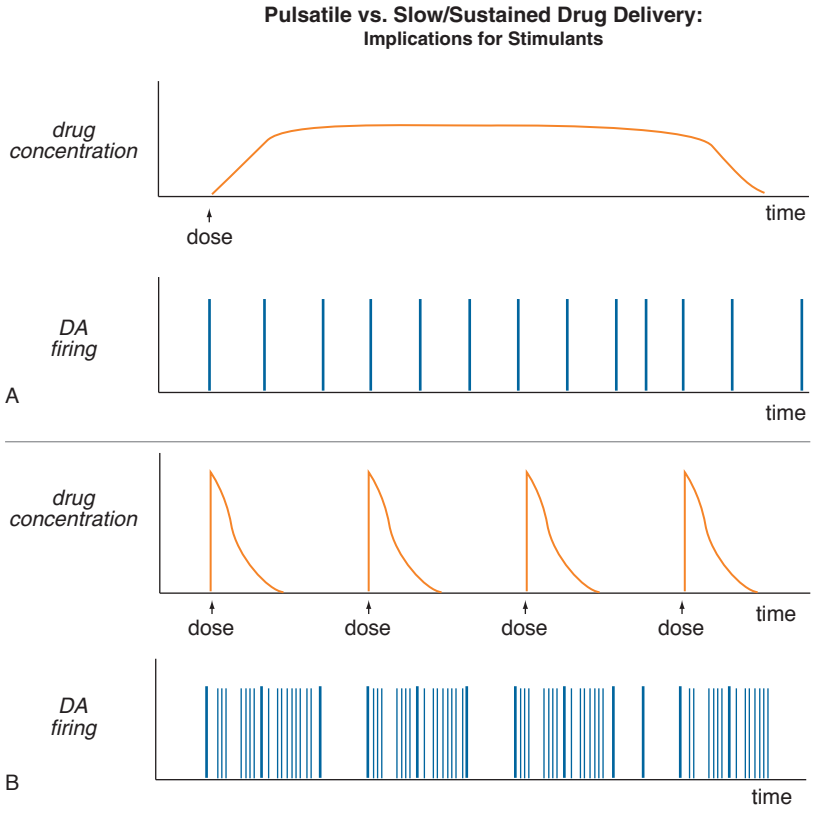

Figure 12-29. Pulsatile versus slow and sustained drug delivery. The difference between stimulants as treatments and stimulants as drugs of abuse lies less in their mechanism of action than in the route of administration and dose, and thus how fast, how completely, and for how long DAT is blocked. When using stimulants to treat a patient it may be preferable to obtain a slow-rising, constant, steady-state level of the drug (A). Under those circumstances the firing pattern of DA will be tonic, regular, and not at the mercy of fluctuating levels of dopamine. 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 (B). Unlike a constant administration of DA, pulsatile administration of DA may lead to the highly reinforcing pleasurable effects of drugs of abuse, and to compulsive use and addiction.

theoretically follow chronic treatment with atomoxetine in Figure 12-33. 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 prefrontal cortex causing an excess of phasic NE and DA activity (Figure 12-12). When slow-onset, long-duration, and essentially perpetual NET inhibition occurs in prefrontal cortex due to atomoxetine, this theoretically restores tonic postsynaptic D_1 and α_{2A}-adrenergic signaling, downregulates phasic NE and DA actions, and desensitizes postsynaptic NE and DA receptors. The possible consequences of this are to reduce chronic HPA axis overactivation and thereby potentially reverse stress-related brain atrophy and even induce neurogenesis that could protect the brain. Such biochemical and molecular changes could be associated with decreases in ADHD symptoms, reduction of relapse, and 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 and SNRIs for the treatment of depression and anxiety. Such possibilities are already indicated by early clinical investigations of this mechanism of selective NRI action in ADHD, but much further work is necessary to establish with certainty the long-term effects of selective NRI action, the differences of outcomes if any compared to long-term stimulant actions, and the best ADHD patient profile to choose for the selective NRI mechanism. 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 have not been previously treated with stimulants, or in ADHD patients who have been treated long-term (longer than 8–12 weeks). NRIs may actually be preferred to stimulants in patients with complex comorbidities.

Alpha-2A-adrenergic agonists

Norepinephrine receptors are discussed in Chapter 6 and illustrated in Figures 6-27 through 6-30. There are numerous subtypes of α-adrenergic receptors, from presynaptic autoreceptors, generally of the α_{2A} subtype (Figures 6-27, 6-28, 6-29) to postsynaptic α_{2A}, α_{2B}, α_{2C}, and α_1 subtypes (Figure 6-27). Alpha-2A receptors are

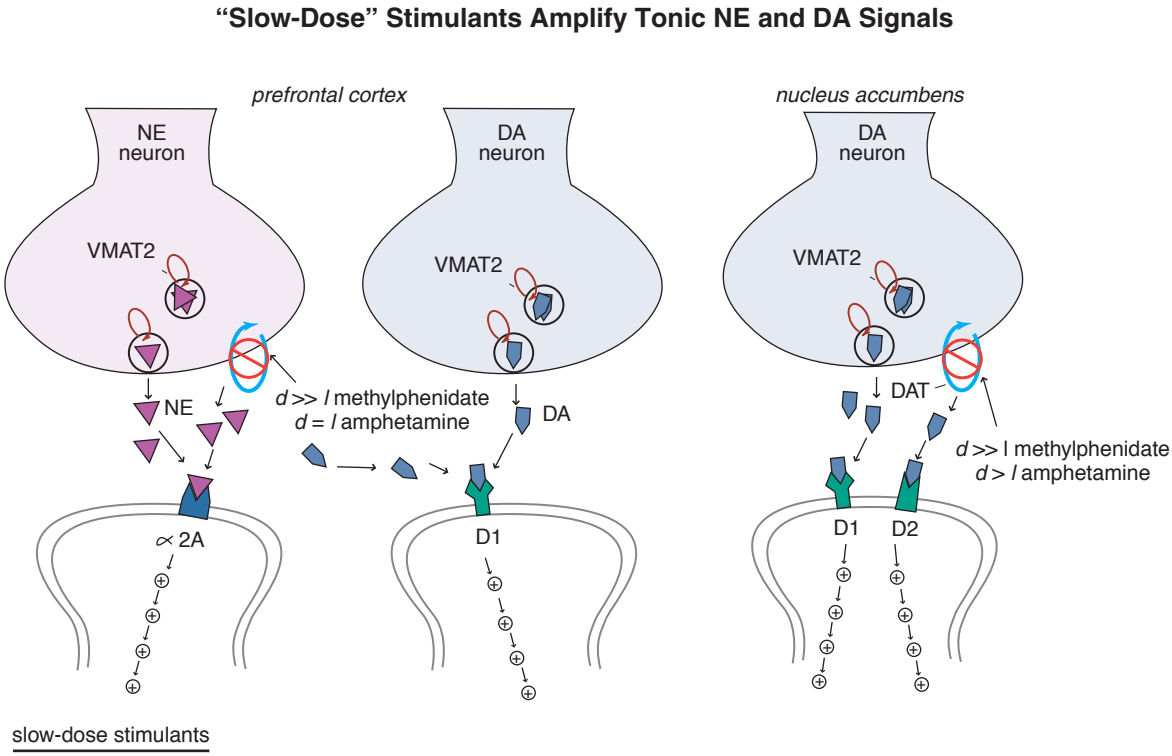

Figure 12-30. Slow-dose stimulants amplify tonic norepinephrine and dopamine signals. Hypothetically, whether a drug has abuse potential depends on how it affects the DA pathway. In other words, the pharmacodynamic and pharmacokinetic properties of stimulants affect their therapeutic as well as their potential abuse profiles. Extended-release formulations of oral stimulants, the transdermal methylphenidate patch, and the new 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 transporter (NET) in the prefrontal cortex and the DA transporter (DAT) in the nucleus accumbens. Hypothetically, the "slow-dose" stimulants occupy NET in the prefrontal cortex with slow enough onset, and for long enough duration, that they enhance tonic NE and DA signaling via α_{2A} and D_1 postsynaptic receptors, respectively, but they do not occupy DAT quickly or extensively enough in the nucleus accumbens to increase phasic signaling via D_2 receptors. The latter hypothetically suggests reduced abuse potential.

widely distributed throughout the CNS, with high levels in the cortex and locus coeruleus. These receptors are thought to be the primary mediators of the effects of NE in 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 α_{2C} receptors are densest in striatum. Alpha-1 receptors generally have opposing actions to α_2 receptors, with α_2 mechanisms predominating when NE release is low or moderate (i.e., for normal attention), but with α_1 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 α_{2A} 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 α_2 receptors used to treat ADHD, guanfacine (Figure 12-35) and clonidine (Figure 12-36). Guanfacine is relatively more selective for α_{2A} receptors (Figure 12-35).

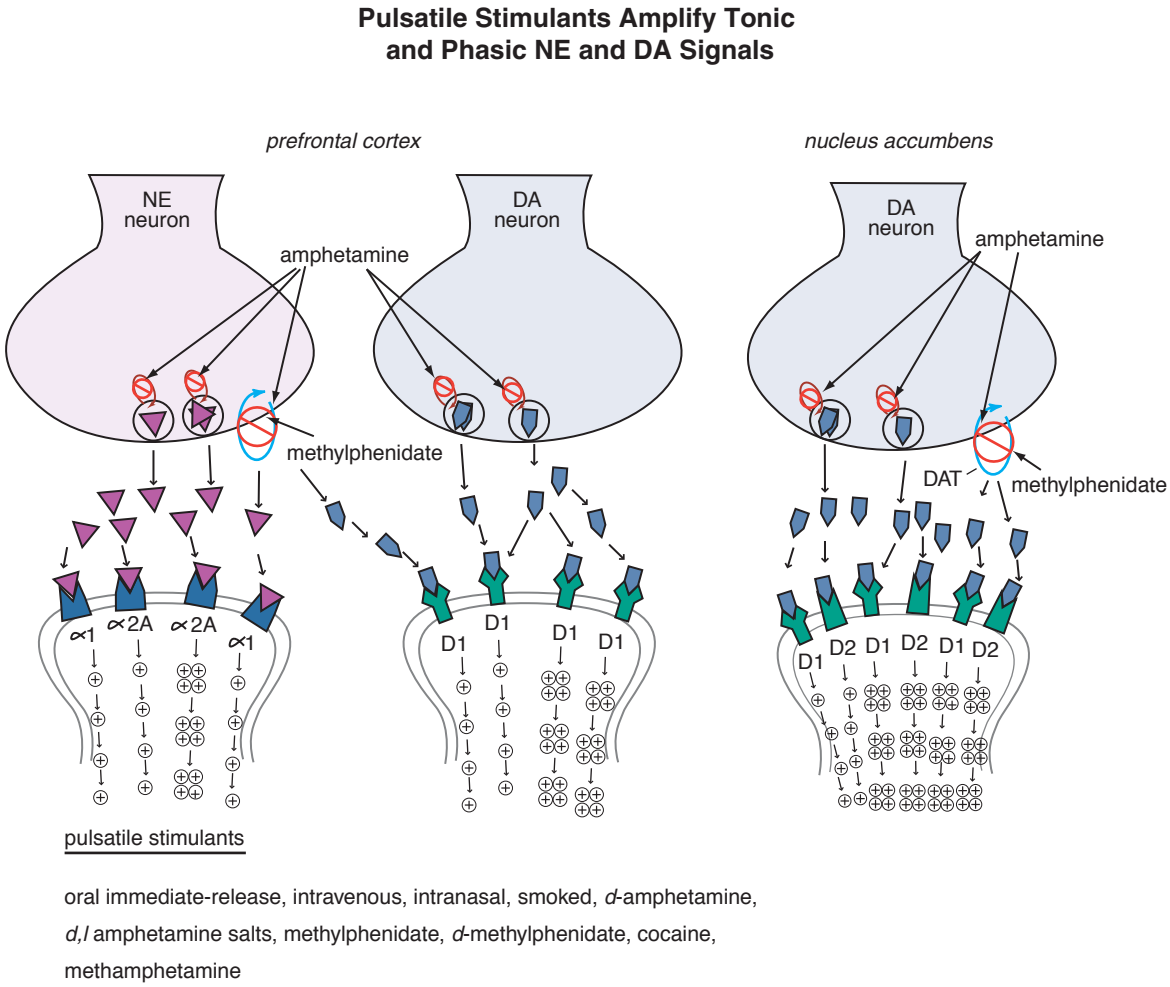

Figure 12-31. Pulsatile stimulants amplify tonic and phasic norepinephrine and dopamine signals. Immediate-release oral stimulants – similarly to intravenous, smoked, or snorted stimulants (which are considered pulsatile stimulants) – lead to a rapid increase in NE and DA levels. Rapidly amplifying the phasic neuronal firing of DA and NE is associated with euphoria and abuse. While methylphenidate and amphetamine have slightly different mechanisms of action, both medications can lead to massive release of DA. This increased release of DA may also contribute to the abuse potential of immediate-release formulations of stimulants, due to increased phasic as well as tonic DA signaling.

Recently, guanfacine 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 α_2 receptors, with actions on α_{2A}, α_{2B}, and α_{2C} receptors (Figure 12-36). In addition, clonidine has actions on imidazoline receptors, thought to be responsible for some of clonidine's sedating and hypotensive actions (Figure 12-37). Although the actions of clonidine at α_{2A} receptors exhibit therapeutic potential for ADHD, its actions at other receptors may increase side effects. Clonidine is approved for the treatment of hypertension, but not for the treatment of ADHD, conduct disorder, oppositional defiant disorder, or Tourette's syndrome, for which it is often used "off-label."

By contrast, the selective α_{2A} receptor agonist guanfacine is 15–60 times more selective for α_{2A} receptors than for α_{2B} and α_{2C} 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

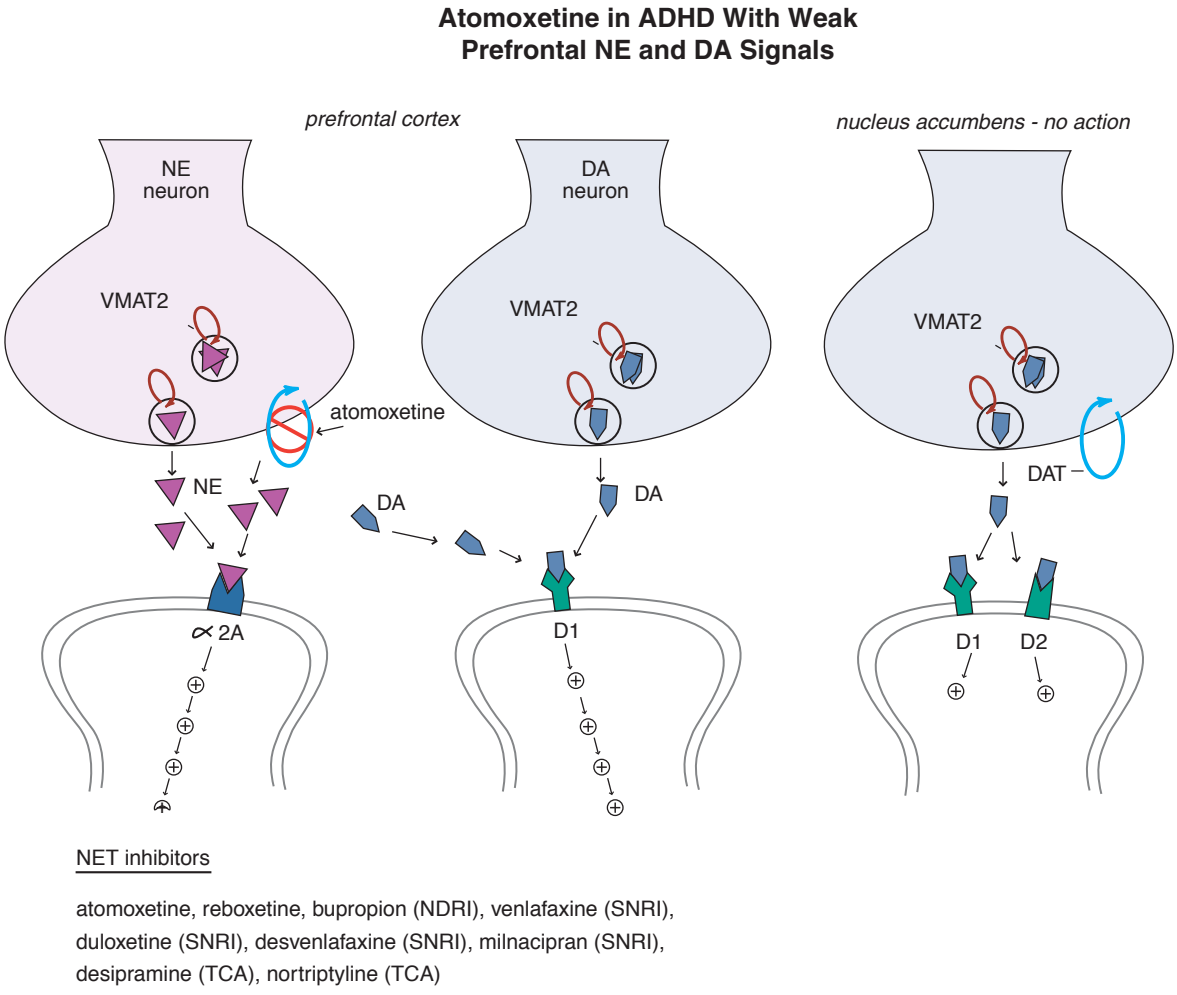

Figure 12-32. Atomoxetine in ADHD with weak prefrontal norepinephrine and dopamine signals. It has been suggested that atomoxetine can have therapeutic effects in ADHD without abuse potential. As a norepinephrine reuptake blocker, atomoxetine causes NE and DA levels to increase in the prefrontal cortex, where inactivation of both of these neurotransmitters is largely due to NET (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). Thus, as shown in Figure 12-22, by increasing NE and DA levels to their optimal levels in the prefrontal cortex (top of the inverted U-shaped curve), atomoxetine may be able to increase attention and decrease hyperactivity in patients with ADHD.

cortical function. Thus, it can be said that guanfacine exhibits therapeutic efficacy with a reduced side-effect profile compared to clonidine. The therapeutic benefits of guanfacine are related to the direct effects of the drug on postsynaptic receptors in the PFC, which lead to the strengthening of network inputs, and to behavioral improvements as seen in Figures 12-38 and 12-39.

Who are the best candidates for monotherapy with guanfacine ER? 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 12-38). This would lead to scrambled signals lost within the background noise, which could be seen behaviorally as hyperactivity, impulsivity, and inattention (Figure 12-38A). In this instance, treatment with a selective α_{2A} agonist would lead to increased signal via direct stimulation of postsynaptic receptors, and this would translate into the patient being able to focus, sit still, and behave adequately (Figure 12-38B). There is currently no way to identify these patients in advance, other than by an empiric trial of guanfacine ER.

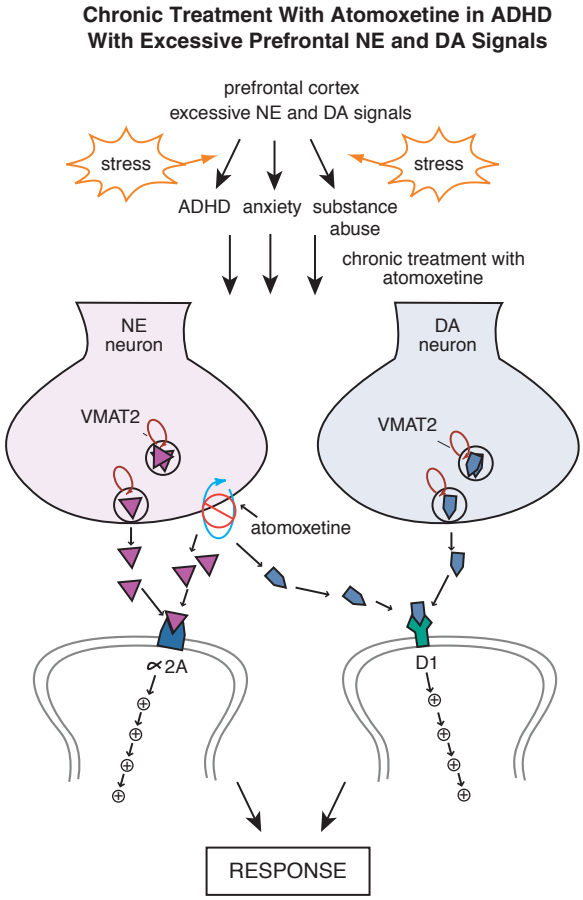

Figure 12-33. Chronic treatment with atomoxetine in ADHD. Stress combined with excessive NE and DA signaling can lead to ADHD, anxiety, or substance abuse. One way to reduce excessive stimulation could be to desensitize postsynaptic DA and NE receptors, and thus allow the neurons to return to normal tonic firing over time. By continuously blocking NET, atomoxetine has the capability of doing this. The "big picture" ramification of such a treatment could be decreased anxiety, decreased heavy drinking, and a reduction in relapses of substance abuse.

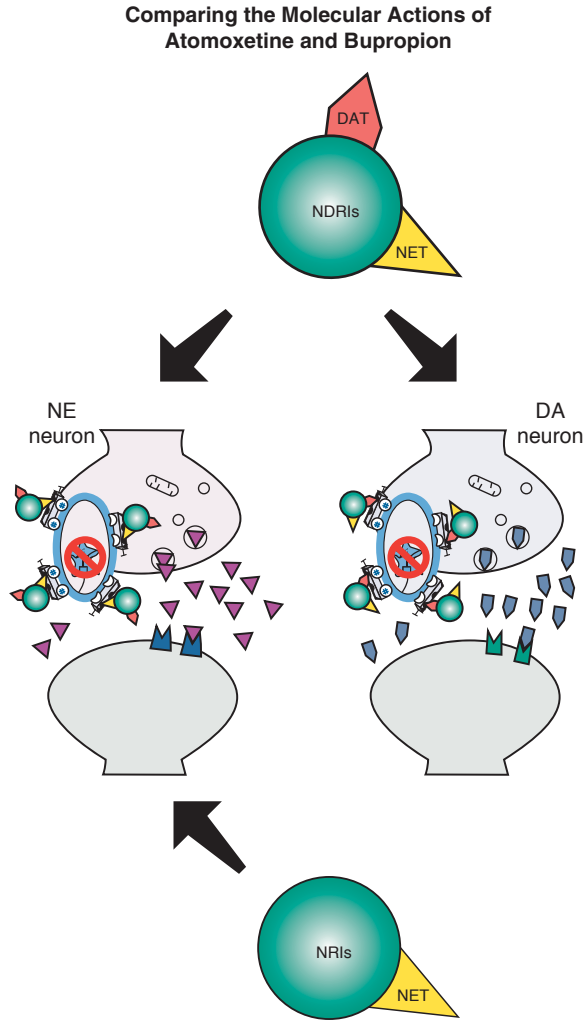

Figure 12-34. Comparing the molecular actions of atomoxetine and bupropion. Atomoxetine is a selective norepinephrine reuptake inhibitor or NRI, while bupropion is a norepinephrine–dopamine reuptake inhibitor or NDRI. Both agents have some pharmacological properties in common, and both of these drugs can have therapeutic effects in the treatment of ADHD.

Patients suffering from ADHD and oppositional symptoms can be argumentative, disobedient, aggressive, and exhibit temper tantrums (Figures 12-8 and 12-39). 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 12-39A). While treatment with a stimulant will improve the situation by reducing the noise, it will not solve the strong NE deficiencies (Figure 12-39B), therefore only partially improving behavior. Augmenting a stimulant with an α_{2A} agonist (Figure 12-39C) will 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 can 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.

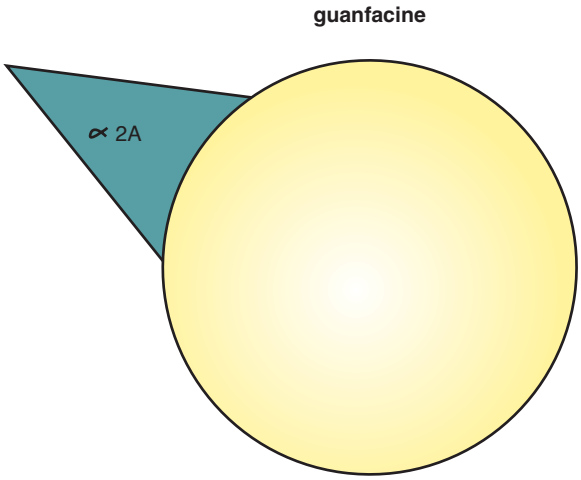

Figure 12-35. Guanfacine. Guanfacine is much more selective for α_{2A} receptors than clonidine and also exhibits therapeutic efficacy with a reduced side-effect profile compared to clonidine. The therapeutic benefits of guanfacine are related to its enhancement of prefrontal cortical functioning, which leads to behavioral improvements. Tolerability and convenience are also enhanced by once-daily oral controlled-release formulation.

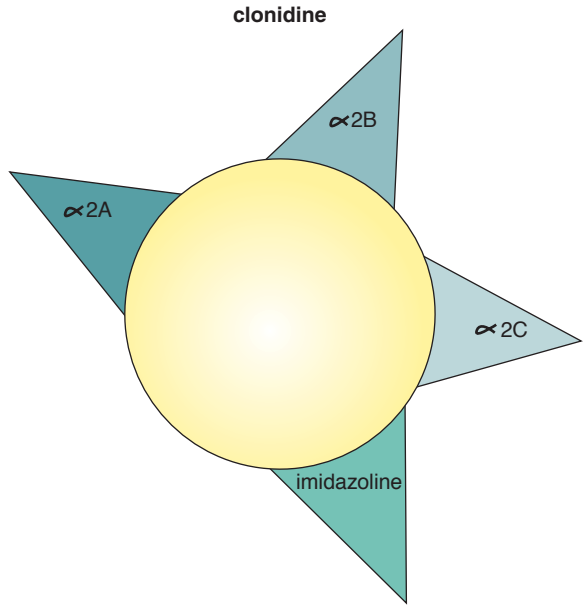

Figure 12-36. Clonidine. The nonselective α_2-adrenergic agonist clonidine binds to α_{2A}, α_{2B}, and α_{2C} receptors. Moreover, clonidine also binds to imidazoline receptors, which contribute to its sedating and hypotensive effects. Clonidine is approved for the treatment of hypertension but is often used "off-label" for the treatment of ADHD, conduct disorder, oppositional defiant disorder, and Tourette's syndrome.

Future treatments for ADHD

Several new mechanisms being targeted for the symptoms of ADHD also are being targeted for cognitive symptoms in other disorders including schizophrenia and Alzheimer's dementia. Enhancing prefrontal cortex histamine actions by blocking its presynaptic H_3 autoreceptor is discussed in Chapter 11 and illustrated in Figure 11-11. Several **H_3 antagonists** are in testing to boost cognitive function in ADHD.

Boosting acetylcholine function in prefrontal cortex is another pro-cognitive approach. Muscarinic agonists tend to be poorly tolerated, but there are several emerging approaches to stimulating nicotinic cholinergic receptors. Several **α_7-nicotinic receptor agonists** are being tested (e.g., EVP-6124, TC5619, DMXB-A/GTS21, MEM3454, R4996/MEM63908, AZD0328, ABT560, JN403, RG3487), some with promising early clinical results in ADHD. Ongoing investigations are dealing with the possible development of tolerance to full agonists without allosteric actions, insufficient efficacy in partial agonists, and how to treat smokers who are already stimulating their nicotinic receptors. One multifunctional agent is RG3487, which is both an α_7-nicotinic partial agonist and a **5HT$_3$ antagonist**, the latter mechanism discussed in Chapter 7 and illustrated in Figure 7-46 as a mechanism to raise acetylcholine levels in the cortex. Vortioxetine, a novel multifunctional antidepressant with 5HT$_3$ antagonist, SERT inhibition, and multiple other pharmacologic actions, discussed in Chapter 7 and illustrated in Figure 7-89, also raises acetylcholine levels in experimental models and has theoretical appeal as a pro-cognitive agent not only in depression but also in other disorders such as ADHD. Agonists for a different nicotinic receptor, the **$\alpha_4\beta_2$-nicotinic receptor**, are discussed in Chapter 14 on substance abuse, and are being tested as well for potential precognitive actions (e.g., varenicline, ABT560, also an $\alpha_4\beta_2$ agonist).

Other early-stage pro-cognitive mechanisms being tested in ADHD and other disorders are **AMPAkines**, boosting glutamate neurotransmission at AMPA receptors (e.g., CX1739, CS717, LY451395), **5HT$_6$ antagonists** (e.g., PRX03140, PRX07034, SAM-315, SAM-531, SB742457, SYN114, SYN120), and phosphodiesterase 4 **(PDE$_4$) inhibitors** (e.g., HT0712).

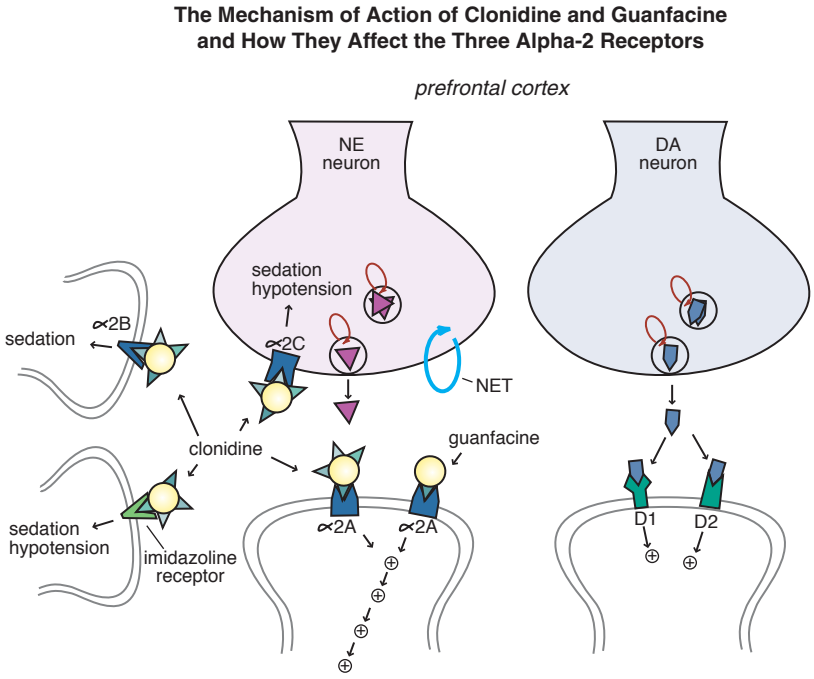

Figure 12-37. Mechanism of action of clonidine and guanfacine. Alpha-2-adrenergic receptors are present in high concentrations in the prefrontal cortex (PFC), but only in low concentrations in the nucleus accumbens. Alpha-2 receptors come in three flavors: α_{2A}, α_{2B}, and α_{2C}. The most prevalent subtype in the prefrontal cortex is the α_{2A} receptor, and these apparently mediate the inattentive, hyperactive, and impulsive symptoms of ADHD by regulating the PFC. 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 PFC. 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.

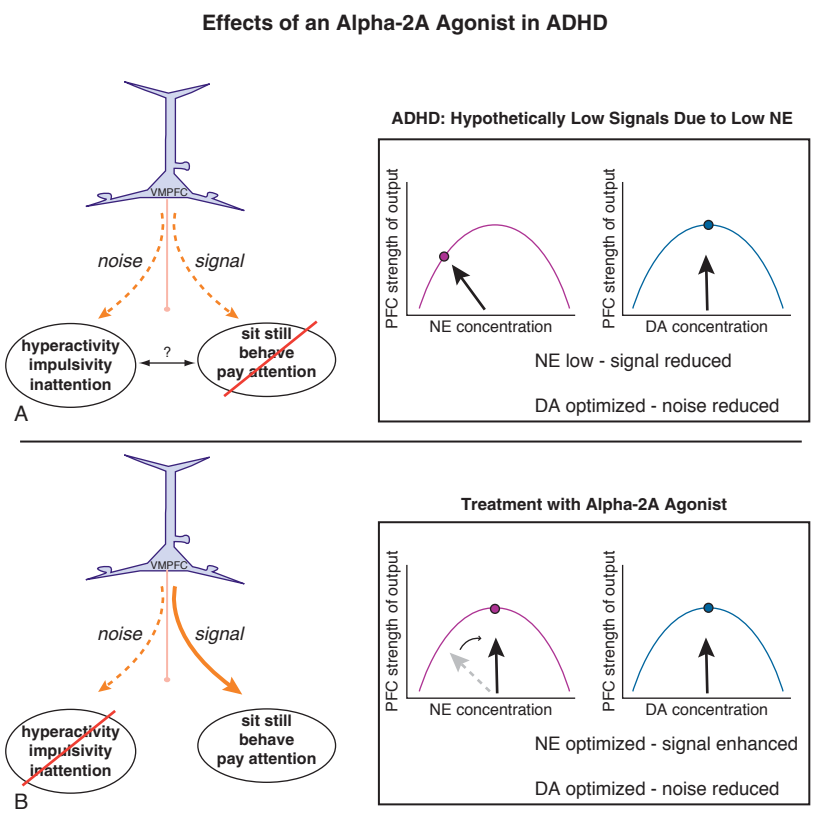

Figure 12-38. Effects of an α_{2A} agonist in ADHD. The symptoms of ADHD could hypothetically be due to low NE levels in the PFC, without additional impairments in DA neurotransmission. The resulting scrambled signals may manifest as hyperactivity, impulsivity, and inattention (A). Treatment with a selective α_{2A} agonist (B) would lead to increased signal via direct stimulation of postsynaptic receptors, resulting in increased ability to sit still and focus.

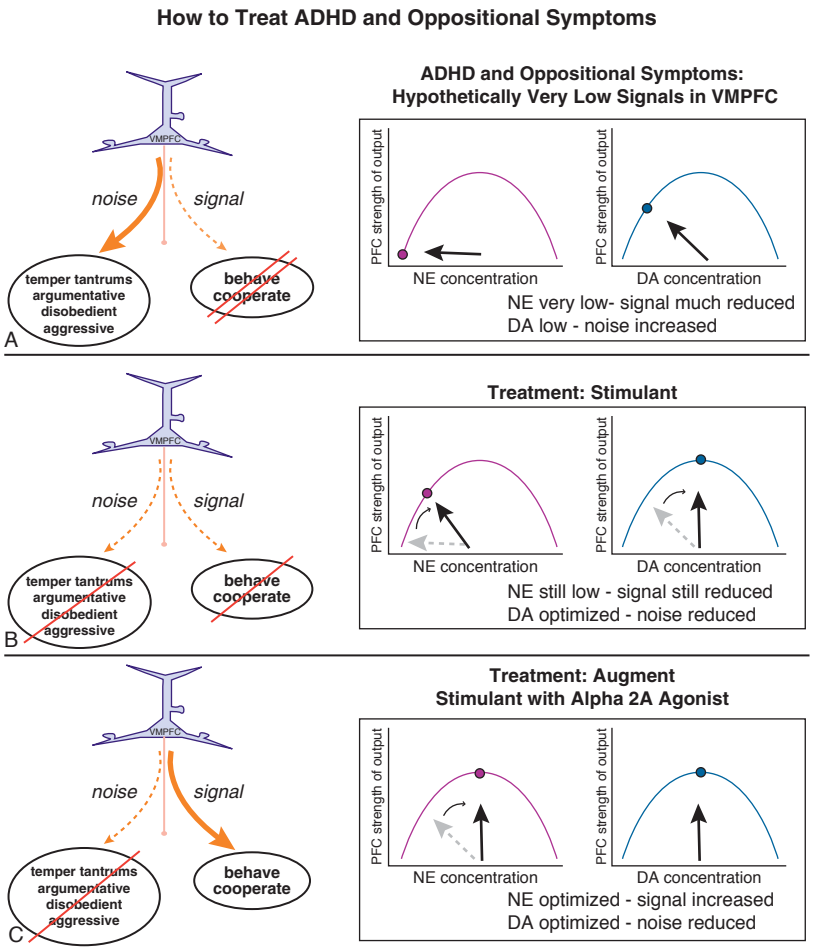

Figure 12-39. How to treat ADHD and oppositional symptoms. Argumentative, disobedient, and aggressive behaviors are often seen in patients suffering from ADHD and oppositional symptoms. These behaviors could theoretically be due to low levels of DA and extensively low levels of NE in the VMPFC in some patients, thus leading to much reduced signal and increased noise (A). While treatment with a stimulant may reduce the noise, it will not solve the strong NE deficiencies (B), therefore only partially improving behavior. The augmentation of a stimulant with an α_{2A} agonist (C) could optimize the levels of NE, thus enhancing the signal, in the presence of an already optimized DA output.

Summary

Attention deficit hyperactivity disorder (ADHD) has core symptoms of inattentiveness, impulsivity, and hyperactivity, linked theoretically to specific malfunctioning neuronal circuits in prefrontal cortex. ADHD can also be conceptualized as a disorder of dysregulation of norepinephrine (NE) and dopamine (DA) in the prefrontal cortex, including some patients with deficient NE and DA and others with excessive NE and DA. Treatments theoretically return patients to normal efficiency of information processing in the prefrontal circuits. Differences exist between children and adults with ADHD, and the special considerations for adults, such as treating comorbidities and using nonstimulants, are receiving increasing attention in psychopharmacology. 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 by stimulants. 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 a novel α_{2A}-adrenergic agonist, guanfacine ER, are also introduced.