01 - 8 Anxiety, Trauma, and Treatment

8 Anxiety, Trauma, and Treatment

Anxiety, Trauma,

and Treatment Symptom Dimensions in Anxiety Disorders 359 When Is Anxiety an Anxiety Disorder? 359 Overlapping Symptoms of Major Depression and Anxiety Disorders 360 Overlapping Symptoms of Different Anxiety Disorders 362 The Amygdala and the Neurobiology of Fear 364 Cortico-Striato-Thalamo-Cortical (CSTC) Loops and the Neurobiology of Worry 365 Benzodiazepines as Drugs for Anxiety 366 Alpha-2-Delta Ligands as Anxiolytics 366 This chapter will provide a brief overview of anxiety disorders, traumatic disorders, and their symptoms and their treatments. Included here are descriptions of how the symptoms of anxiety disorders overlap with each other, and also with the symptoms of major depressive disorder and with the symptoms of trauma and stressrelated disorders. Clinical descriptions and formal diagnostic criteria are mentioned here only in passing. The reader should consult standard reference sources for this material. The discussion here will emphasize how the functioning of various brain circuits and neurotransmitters – especially those centered on the amygdala – impact our understanding of the symptoms of fear, worry, and traumatic memories. The goal of this chapter is to acquaint the reader with ideas about the clinical and biological aspects of anxiety/traumatic symptoms in order to understand the mechanisms of action of the various treatments. Many of the psychopharmacological treatments are extensively discussed in other chapters. For details of mechanisms of the many agents used to treat anxiety that are also used to treat unipolar depression (monoamine reuptake inhibitors), the reader is referred to Chapter 7 on mood disorders and their treatments; for those agents used to treat anxiety and traumatic disorders that are also used to treat chronic pain (i.e., certain ion-channel-inhibiting anticonvulsants), the reader is referred to Chapter 9 on chronic pain Serotonin and Anxiety 368 Noradrenergic Hyperactivity in Anxiety 370 Fear Conditioning versus Fear Extinction 370 Novel Approaches to the Treatment of Anxiety Disorders 374 Treatments for Anxiety Disorder Subtypes 377 Generalized Anxiety Disorder 377 Panic Disorder 377 Social Anxiety Disorder 377 PTSD 377 Summary 378 and its treatment. Although all psychiatric disorders can benefit from psychotherapy, anxiety/traumatic disorders may be especially effectively treated with psychotherapy. In many cases, psychotherapy for anxiety disorders can be even more effective

than drug treatment or can enhance the efficacy of anxiolytic agents. Novel psychotherapies aiming to prevent or reverse fear conditioning and fear reconsolidation are mentioned briefly here but for more details of psychotherapy for anxiety, the reader is referred to general psychiatry and clinical psychology texts as well as to books by the author that cover both psychopharmacology and psychotherapy (see reference list). The discussion of anxiety and its disorders in this chapter emphasizes the neurobiology of anxiety and the mechanism of action of drugs for anxiety. The reader should consult standard drug handbooks (such as Stahl's Essential Psychopharmacology: the Prescriber's Guide) for details of doses, side effects, drug interactions, and other issues relevant to the prescribing of these drugs in clinical practice. SYMPTOM DIMENSIONS IN ANXIETY DISORDERS When Is Anxiety an Anxiety Disorder? Anxiety is a normal emotion under circumstances of threat and is thought to be part of the evolutionary "fight 359

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY or flight" reaction of survival. Whereas it may be normal or even adaptive to be anxious when a saber-tooth tiger (or its modern-day equivalent) is attacking, there are many circumstances in which the presence of anxiety is maladaptive or excessive and constitutes a psychiatric disorder. The idea of anxiety as a psychiatric disorder is evolving rapidly, and is characterized by the concept of core symptoms of excessive fear and worry (symptoms at the center of anxiety disorders in Figure 8-1), compared to major depression, which is characterized by core symptoms of depressed mood or loss of interest (symptoms at the center of major depressive disorder in Figure 8-1). Some disorders associated with the symptoms of anxiety such as obsessive–compulsive disorder (OCD) are no longer classified as anxiety disorders in some diagnostic manuals, and here OCD is discussed in Chapter 13 on impulsive and compulsive disorders. Other disorders associated with the symptoms of anxiety such as posttraumatic stress disorder (PTSD) are also no longer classified as anxiety disorders in certain diagnostic manuals, but are discussed here in this chapter. Anxiety disorders have considerable symptom overlap with major depression (see those symptoms surrounding core features shown in Figure 8-1), particularly sleep disturbance, problems concentrating, and fatigue and psychomotor/arousal symptoms. Each anxiety disorder also has a great deal of symptom overlap with other anxiety disorders (Figures 8-2 through 8-5; see also Figure 13-30). Anxiety disorders are also extensively comorbid, not only with major depression, but also with each other, since many patients qualify over time for a second or even third concomitant anxiety disorder (Figures 8-2 through 8-5). Finally, anxiety disorders are frequently comorbid with many other conditions such as substance abuse, Overlap of Major Depressive Disorder and Anxiety Disorders fatigue psychomotor arousal concentration concentration depressed mood anxiety interest/ pleasure guilt/ worthlessness sleep sleep appetite/ weight suicidality major depressive disorder attention deficit hyperactivity disorder (ADHD), bipolar disorder, pain disorders, sleep disorders, and more. So, what is an anxiety disorder? These disorders all seem to maintain the core features of some form of anxiety or fear coupled with some form of worry, but their natural history over time shows them to morph from one into another, to evolve into full syndrome expression of anxiety-disorder symptoms (Figure 8-1) and then to recede into subsyndromal levels of symptoms, only to reappear again as the original anxiety disorder, a different anxiety disorder (Figures 8-2 through 8-5), or major depression (Figure 8-1). If anxiety disorders all share core symptoms of fear and worry (Figures 8-1 and 8-6) – and as we shall see later in this chapter, are all basically treated with the same drugs, including many of the same drugs that treat major depression – the question now arises as to what the difference is between one anxiety disorder and another. Also, one could ask what the difference is between major depression and anxiety disorders. Are all these entities really different disorders or are they instead

different aspects of the same illness? Overlapping Symptoms of Major Depression and Anxiety Disorders Although the core symptoms of major depression (depressed mood or loss of interest) differ from the core symptoms of anxiety disorders (fear and worry), there is a great deal of overlap with the other symptoms considered diagnostic for both a major depression episode and for several different anxiety disorders (Figure 8-1). These overlapping symptoms include problems with sleep, concentration, and fatigue as well as psychomotor/ arousal symptoms (Figure 8-1). It is thus easy to see how the gain or loss of just a few additional symptoms can morph a major depressive episode into an anxiety Figure 8-1 Overlap of major depressive disorder and anxiety disorders. Although the core symptoms of anxiety disorders (anxiety and worry) differ from the core symptoms of major depression (loss of interest and depressed mood), there is considerable overlap among the rest of the symptoms associated with these disorders (compare the “anxiety disorders” puzzle on the right to the “major depressive disorder” puzzle on the left). For example, fatigue, sleep difficulties, problems concentrating, and psychomotor/arousal symptoms are common to both types of disorders. fatigue panic attacks worry phobic avoidance compulsions irritability muscle tension anxiety disorders

generalized anxiety disorder fatigue concentration generalized anxiety/ fear generalized worry sleep irritability muscle tension panic disorder anticipatory anxiety/ fear worry about panic attacks disorder (Figure 8-1) or one anxiety disorder into another (Figures 8-2 through 8-5). From a therapeutic point of view, it may matter little what the specific diagnosis is across this spectrum of disorders (Figures 8-1 through 8-5). That is, psychopharmacological treatments may not be much different for a patient who currently qualifies for a major depressive episode plus the symptom of anxiety (but not an anxiety disorder) versus a patient who currently qualifies for a major depressive episode plus a comorbid anxiety disorder. Although it can be useful to make specific diagnoses for following patients over time and for documenting the evolution of symptoms, Chapter 8: Anxiety, Trauma, and Treatment Figure 8-2 Generalized anxiety disorder. The symptoms typically associated with generalized anxiety disorder are shown here. These include the core symptoms of generalized anxiety and worry as well as increased arousal, fatigue, difficulty concentrating, sleep problems, irritability, and muscle tension. Many of these symptoms, including the core symptoms, are present in other anxiety disorders as well. arousal Figure 8-3 Panic disorder. The characteristic symptoms of panic disorder are shown here and include the core symptoms of anticipatory anxiety as well as worry about panic attacks; associated symptoms are the unexpected panic attacks themselves and phobic avoidance or other behavioral changes associated with concern over panic attacks. unexpected panic attacks phobic avoidance/ behavioral change the emphasis from a psychopharmacological point of view is increasingly to take a symptom-based therapeutic strategy for patients with any of these disorders because the brain is not organized according to the DSM, but according to brain circuits with topographical localization of function. That is, specific treatments can be tailored to the individual patient by deconstructing whatever disorder the patient has into a list of the specific symptoms a given patient is experiencing (see Figures 8-2 through 8-5). These symptoms are then matched to hypothetically malfunctioning brain circuits, regulated by specific neurotransmitters, in order to rationally select and 361

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY social anxiety disorder fatigue concentration social/ performance anxiety/ fear worry about exposure sleep PTSD anxiety/ reexperiencing worry sleep combine psychopharmacological treatments to eliminate symptoms by increasing the efficiency of information processing in the malfunctioning brain circuits, and thereby get the patient into

remission. This was discussed extensively in Chapter 6 on mood disorders and illustrated in Figures 6-42 through 6-44. Overlapping Symptoms of Different Anxiety Disorders Although there are different diagnostic criteria for different anxiety disorders (Figures 8-2 through 8-5), these are constantly changing and many do not even consider OCD or PTSD to be anxiety disorders any longer (OCD is discussed in Chapter 13 on impulsivity). All anxiety disorders have overlapping symptoms of anxiety/ Figure 8-4 Social anxiety disorder.

Symptoms of social anxiety disorder, shown here, include the core symptoms of anxiety or fear over social performance plus worry about social exposure. Associated symptoms are panic attacks that are predictable and expected in certain social situations as well as phobic avoidance of those situations. arousal expected panic attacks phobic avoidance/ behavioral change Figure 8-5 Posttraumatic stress disorder (PTSD). The characteristic symptoms of PTSD are shown here. These include the core symptoms of anxiety while the traumatic event is being re-experienced as well as worry about having the other symptoms of PTSD, such as increased arousal and startle responses, sleep difficulties including nightmares, and avoidance behaviors. PTSD is now categorized as a stress-related disorder rather than as an anxiety disorder, and is considered a disorder of hyperarousal. arousal avoidance fear coupled with worry (Figure 8-6). Remarkable progress has been made in understanding the circuitry underlying the core symptom of anxiety/fear based upon an explosion of neurobiological research on the amygdala (Figures 8-7 through 8-14). The links between the amygdala, fear circuits, and treatments for the symptom of anxiety/fear across the spectrum of anxiety, trauma, and stress disorders are discussed throughout the rest of this chapter. Worry is the second core symptom shared across the spectrum of anxiety disorders (Figure 8-7). This symptom is hypothetically linked to the functioning of cortico-striato-thalamo-cortical(CSTC) loops. The links between the CSTC “worry loops” and treatments

Anxiety: The Phenotype deconstruct the syndrome… anxiety …into symptoms Associate Symptoms of Anxiety with Brain Regions and Circuits That Regulate Them fear

- panic
- phobia worry
- anxious misery
- apprehensive expectation
- obsessions cortico-striatothalamo-cortical circuit for the symptom of worry across the spectrum of anxiety disorders are discussed later in this chapter (see also Figures 8-15 through 8-20). We shall see that what differentiates one anxiety disorder from another may not be the anatomical localization or the neurotransmitters regulating fear and worry in each of these disorders (Figures 8-6 and 8-7), but the specific nature of malfunctioning within these same circuits in various anxiety disorders. That is, in generalized Chapter 8: Anxiety, Trauma, and Treatment Figure 8-6 Anxiety: the phenotype.

Anxiety can be deconstructed, or broken down, into the two core symptoms of fear and worry. These symptoms are present in all anxiety disorders, although what triggers them may differ from one disorder to the next. fear

- panic
- phobia worry

- anxious misery
- apprehensive expectation
- obsessions Figure 8-7 Linking anxiety symptoms to circuits. Anxiety and fear symptoms (e.g., panic, phobias) are regulated by an amygdala-centered circuit. Worry, on the other hand, is regulated by a cortico-striato-thalamo-cortical (CSTC) circuit. These circuits may be involved in all anxiety disorders, with the different phenotypes reflecting not unique circuitry but rather divergent malfunctioning within those circuits. amygdala-centered circuit anxiety disorder, malfunctioning in the amygdala and CSTC worry loops may be hypothetically persistent, and unremitting, yet not severe (Figure 8-2), whereas malfunctioning may be theoretically intermittent but catastrophic in an unexpected manner for panic disorder (Figure 8-3) or in an expected manner for social anxiety (Figure 8-4). Circuit malfunctioning may be traumatic in origin and conditioned in PTSD (Figure 8-5). 363

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY THE AMYGDALA AND THE NEUROBIOLOGY OF FEAR The amygdala, an almond-shaped brain center located near the hippocampus, has important anatomical connections that allow it to integrate sensory and cognitive information, and then determine whether there will be a fear response. Specifically, the affect or feeling of fear may be regulated via the reciprocal connections the amygdala shares with key areas of prefrontal cortex that regulate emotions, namely the orbitofrontal cortex and the anterior cingulate cortex (Figure 8-8). However, fear is not just a feeling. The fear response can also include motor responses. Depending upon the circumstances and one's temperament, those motor responses could be fight, flight, or freezing in place. Motor responses of fear are regulated in part by connections between the amygdala and the periaqueductal gray area of the brainstem (Figure 8-9). There are also endocrine reactions that accompany fear, in part due to connections between the amygdala and the hypothalamus, causing changes in the HPA (hypothalamic-pituitary-adrenal) axis, and thus of cortisol levels. A quick boost of cortisol may enhance survival when encountering a real, but short-term, Affect of Fear ACC OFC amygdala d overactivation fear Figure 8-8 Affect of fear. Feelings of fear are regulated by reciprocal connections between the amygdala and the anterior cingulate cortex (ACC) and the amygdala and the orbitofrontal cortex (OFC). Specifically, it may be that overactivation of these circuits produces feelings of fear. threat. However, chronic and persistent activation of this aspect of the fear response can lead to increased medical comorbidity, including increased rates of coronary artery disease, type 2 diabetes, and stroke (Figure 8-10), and also potentially to hippocampal atrophy, as discussed in Chapter 6 and shown in Figure 6-30. Breathing can also change during a fear response, regulated in part by the connections between the amygdala and the parabrachial nucleus in the brainstem (Figure 8-11). An adaptive response to fear is to accelerate respiratory rate when having a fight/flight reaction to enhance survival, but, in excess, this can lead to unwanted symptoms of shortness of breath, exacerbation of asthma, or a false sense of being smothered (Figure 8-11), all symptoms common during anxiety, and especially during attacks of anxiety such as panic attacks. The autonomic nervous system is attuned to fear, and is able to trigger responses from the cardiovascular system, such as increased pulse and blood pressure for fight/flight reactions and survival during real threats. These autonomic and cardiovascular responses are mediated by connections between the amygdala and the locus coeruleus, home of the noradrenergic cell bodies (Figure 8-12; noradrenergic neurons are discussed in Avoidance PAG amygdala d fear response motor responses overactivation periaqueductal gray fight/flight or freeze Figure 8-9 Motor responses of fear. Feelings of fear may

be expressed through behaviors such as avoidance, which is partly regulated by reciprocal connections between the amygdala and the periaqueductal gray (PAG). Avoidance in this sense is a motor response and may be analogous to freezing under threat. Other motor responses are to fight or to run away (flight) in order to survive threats from the environment.

Endocrine Output of Fear hypothalamus amygdala d fear response overactivation endocrine hypothalamus cortisol coronary artery disease type 2 diabetes stroke Figure 8-10 Endocrine output of fear. The fear response may be characterized in part by endocrine effects such as increases in cortisol, which occur because of amygdala activation of the hypothalamic-pituitary-adrenal (HPA) axis. Prolonged HPA activation and cortisol release can have significant health implications, such as increased risk of coronary artery disease, type 2 diabetes, and stroke. Chapter 6 and noradrenergic pathways and neurons are illustrated in Figures 6-12 through 6-16). When autonomic responses are repetitive, inappropriately or chronically triggered as part of an anxiety disorder, this can lead to increases in atherosclerosis, cardiac ischemia, hypertension, myocardial infarction, and even sudden death (Figure 8-12). “Scared to death” may not always be an exaggeration or a figure of speech! Finally, anxiety can be triggered internally from traumatic memories stored in the hippocampus and activated by connections with the amygdala (Figure 8-13), especially in conditions such as PTSD. The processing of the fear response is regulated by the numerous neuronal connections flowing into and out of the amygdala. Each connection utilizes specific neurotransmitters acting at specific receptors (Figure 8-14). What is known about these connections is not only that several neurotransmitters are involved in the production of symptoms of anxiety at the level of the amygdala, but that numerous anxiolytic drugs have actions upon these specific neurotransmitter systems to relieve the symptoms of anxiety and fear (Figure 8-14). The known neurobiological regulators of the amygdala Chapter 8: Anxiety, Trauma, and Treatment Breathing Output amygdala PBN d fear response overactivation respiratory parabrachial nucleus respiratory rate shortness of breath asthma Figure 8-11 Breathing output. Changes in respiration may occur during a fear response; these changes are regulated by activation of the parabrachial nucleus (PBN) via the amygdala. Inappropriate or excessive activation of the PBN can lead not only to increases in the rate of respiration but also to symptoms such as shortness of breath, exacerbation of asthma, or a sense of being smothered. include the neurotransmitters GABA, serotonin, and norepinephrine, and the voltage-gated calcium channels. Not surprisingly, known anxiolytics act upon these same neurotransmitters hypothetically in order to mediate their therapeutic actions. CORTICO-STRIATO-THALAMOCORTICAL (CSTC) LOOPS AND THE NEUROBIOLOGY OF WORRY The second core symptom of anxiety disorders, namely, worry, hypothetically involves another unique circuit (Figure 8-15). Worry, which can include anxious misery, apprehensive expectations, catastrophic thinking, and obsessions, is hypothetically linked to CSTC feedback loops from the prefrontal cortex (Figure 8-15 and Figure 8-16). Some experts theorize that similar CSTC feedback loops regulate the related symptoms of ruminations, obsessions, and delusions, all of these symptoms being types of recurrent thoughts. Several neurotransmitters and regulators are known to modulate these circuits, including serotonin, GABA, dopamine, norepinephrine, 365

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Autonomic Output of Fear LC C amygdala d fear response overactivation cardiovascular locus coeruleus atherosclerosis cardiac ischemia BP HR variability MI sudden death Figure 8-12 Autonomic output of fear. Autonomic responses are typically associated with feelings of fear. These include increases in heart rate (HR) and blood

pressure (BP), which are regulated by reciprocal connections between the amygdala and the locus coeruleus (LC). Long-term activation of this circuit may lead to increased risk of atherosclerosis, cardiac ischemia, change in BP, decreased HR variability, myocardial infarction (MI), or even sudden death. glutamate, and voltage-gated ion channels (Figure 8-15), greatly overlapping with many of the same neurotransmitters and regulators known to modulate the amygdala (Figure 8-14). BENZODIAZEPINES AS DRUGS FOR ANXIETY A simplified notion of how benzodiazepines might modulate excessive output from the amygdala during fear responses in anxiety disorders is shown in Figure 8-18. Excessive amygdala activity (shown in Figures 8-8 through Figure 8-12 and in Figure 8-17A) is theoretically reduced by benzodiazepines. These agents enhance phasic inhibition of GABA (γ-aminobutyric acid) by positive allosteric modulation of postsynaptic GABAA receptors (see Chapter 6 for explanation of positive allosteric modulation by benzodiazepines at GABAA receptors and Figures 6-20 through 6-23). The anxiolytic actions of benzodiazepines are hypothetically at GABAA receptors localized within the amygdala, where The Hippocampus: An Internal Fearmonger amygdala hippocampus Figure 8-13 The hippocampus and re-experiencing. Anxiety can be triggered not only by an external stimulus but also by an individual’s memories. Traumatic memories stored in the hippocampus can activate the amygdala, causing the amygdala, in turn, to activate other brain regions and generate a fear response. This is termed re-experiencing and is a particular feature of posttraumatic stress disorder. benzodiazepines hypothetically blunt fear-associated outputs, thereby reducing the symptom of fear (Figure 8-17B). Benzodiazepines interacting at subtypes of GABAA receptors are discussed in Chapter 6 and illustrated in Figures 6-19 through 6-23. Benzodiazepines also theoretically modulate excessive output from worry loops (Figure 8-18A) by enhancing the actions of inhibitory interneurons in CSTC circuits (Figure 8-18B), thereby reducing the symptom of worry. ALPHA-2-DELTA LIGANDS AS ANXIOLYTICS We have discussed voltage-sensitive calcium channels (VSCCs) in Chapter 3 and have illustrated presynaptic N and P/Q subtypes of VSCCs and their role in excitatory neurotransmitter release (see Figures 3-18 and 3-22 through 3-24). Gabapentin and pregabalin, also known as α2δ ligands since they bind to the α2δ subunit of presynaptic N and P/Q VSCCs, block the release of excitatory neurotransmitters such as glutamate that occurs when neurotransmission is excessive, as postulated in the amygdala to cause fear (Figure 8-17A) and in CSTC circuits to cause worry (Figure 8-18A). Hypothetically, α2δ ligands bind to open, overly active VSCCs in the amygdala (Figure 8-17C) to reduce fear, and in CSTC circuits (Figure 8-18C) to reduce worry. The α2δ ligands pregabalin and

Associate Symptoms with Brain Regions, Circuits, and Neurotransmitters That Regulate Them GABA 5HT amygdala-centered circuit fear

- panic
- phobia voltage-gated ion channels Associate Symptoms with Brain Regions, Circuits, and Neurotransmitters That Regulate Them GABA 5HT cortico-striatothalamo-cortical circuit “worry loop” worry
- anxious misery
- apprehensive expectation
- obsessions voltage-gated ion channels Affect of Fear Worry/Obsessions DLPFC FC thalamus striatum overactivation Chapter 8: Anxiety, Trauma, and Treatment Figure 8-14 Linking anxiety symptoms to circuits to neurotransmitters.

Symptoms of anxiety/fear are associated with malfunctioning of amygdala-centered circuits; the neurotransmitters that regulate these circuits include serotonin (5HT), γ-aminobutyric acid (GABA), glutamate, corticotropin releasing factor (CRF), and norepinephrine (NE), among others. In addition, voltage-gated ion channels are involved in neurotransmission within these circuits. glutamate CRF/HPA NE Figure 8-15 Linking worry symptoms to circuits to neurotransmitters.

Symptoms of worry, such as anxious misery, apprehensive expectations, catastrophic thinking, and obsessions, are associated with malfunctioning of cortico-striato-thalamo-cortical loops, which are regulated by serotonin (5HT), γ-aminobutyric acid (GABA), dopamine (DA), norepinephrine (NE), glutamate, and voltage-gated ion channels. DA NE glutamate Figure 8-16 Worry/obsessions circuit. Shown here is a cortico-striatothalamo-cortical loop originating and ending in the dorsolateral prefrontal cortex (DLPFC). Overactivation of this circuit may lead to worry or obsessions. $ worry

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Hyperactive Amygdala and Fear PAG hypothalamus ACC LC OFC amygdala d PBN A FEAR Therapeutic Actions of Benzodiazepines α 2 action δ areas of normalized activation GABA action GABA

neuron B C δ α FEAR Therapeutic Actions of Serotonergic Agents 5HT neuron areas of normalized activation 5HT action FEAR D gabapentin have demonstrated anxiolytic actions in social anxiety disorder and panic disorder, are approved for the treatment of anxiety in some countries, and are also proven to be effective for

the treatment of epilepsy and certain pain conditions, including neuropathic pain and fibromyalgia. The actions of α2δ ligands on VSCCs are discussed and illustrated in Chapter 9 on pain. Alpha-2delta ligands clearly have different mechanisms of action compared to selective serotonin reuptake inhibitors (SSRIs) or benzodiazepines,

and thus can be useful for patients who do not do well on SSRIs/SNRIs (serotonin–norepinephrine reuptake inhibitors) or benzodiazepines. Also, α2δ ligands can be useful to combine with SSRIs/ SNRIs or benzodiazepines in patients who are partial responders and are not in remission. SEROTONIN AND ANXIETY Since the

symptoms, circuits, and neurotransmitters linked to anxiety disorders overlap extensively with those for major depressive disorder (Figure 8-1), it is not surprising that many drugs developed as drugs for depression have Figure 8-17 Potential therapeutic actions of medications on anxiety/ fear. (A) Pathological anxiety/fear may be caused

by overactivation of amygdala circuits. (B) GABAergic agents such as benzodiazepines may alleviate anxiety/fear by enhancing phasic inhibitory actions at postsynaptic GABAA receptors within the amygdala. (C) Agents that bind to the α2δ subunit of presynaptic N and P/Q voltagesensitive calcium channels can block the

excessive release of glutamate in the amygdala and thereby reduce the symptoms of anxiety. (D) The amygdala receives input from serotonergic neurons, which can have an inhibitory effect on some of its outputs. Thus, serotonergic agents may alleviate anxiety/fear by enhancing serotonin input to the amygdala. areas of

overactivation Therapeutic Actions of Alpha-2-Delta Ligands areas of normalized activation 2 action

ligand FEAR proven to be effective treatments for anxiety disorders. Indeed, the leading treatments

for anxiety disorders today are increasingly drugs originally developed as drugs for depression. Serotonin is a key neurotransmitter that innervates the amygdala as well as all the elements of CSTC circuits, namely, the prefrontal cortex, striatum, and thalamus, and thus is poised to regulate both the symptoms of fear and worry (serotonin pathways are discussed in Chapters 5 and 6 and illustrated in Figure 6-40). Most of the drugs for depression that can increase serotonin output by blocking the serotonin transporter (SERT) are also effective in reducing symptoms of anxiety and fear in one or another of the anxiety/trauma disorders illustrated in Figures 8-2 through 8-5, namely, generalized anxiety disorder, panic disorder, social anxiety disorder, and PTSD (and also OCD in Figure 13-30). Such agents include the well-known SSRIs (in Chapter 7, with their mechanism of action illustrated in Figures 7-11 through 7-15), as well as the SNRIs (serotonin–norepinephrine reuptake inhibitors; also discussed in Chapter 7, with their mechanism of action illustrated in Figure 7-32 and Figures 7-11 through 7-15).

Chapter 8: Anxiety, Trauma, and Treatment Figure 8-18 Potential therapeutic actions of medications on worry. (A) Pathological worry may be caused by overactivation of corticostriato-thalamo-cortical (CSTC) circuits. (B) GABAergic agents such as benzodiazepines may alleviate worry by enhancing the actions of inhibitory GABA interneurons within the prefrontal cortex. (C) Agents that bind to the α2δ subunit of presynaptic N and P/Q voltagesensitive calcium channels can block the excessive release of glutamate in CSTC circuits and thereby reduce the symptoms of worry. (D) The prefrontal cortex, striatum, and thalamus receive input from serotonergic neurons, which can have an inhibitory effect on output. Thus, serotonergic agents may alleviate worry by enhancing serotonin (5HT) input within CSTC circuits. Affect of Fear GABA neuron worry worry A B Hyperactive CSTC Circuits and Worry Therapeutic Actions of Benzodiazepines D worry Therapeutic Actions of Serotonergic Agents 5HT neuron C worry Therapeutic Actions of Alpha-2-Delta Ligands action

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY A serotonin 1A (5HT1A) partial agonist, buspirone, is recognized as a drug for generalized anxiety disorder, but not for treatment of the other anxiety/trauma disorder subtypes. 5HT1A partial agonists as augmenting agents to drugs for

depressions are mentioned also in Chapter 7, as are drugs for depression that combine 5HT1A partial agonism with serotonin reuptake inhibition (i.e., serotonin partial agonist reuptake inhibitors [SPARIs] and vilazodone, see Figures 7-23 through 7-27), which should theoretically have anxiolytic actions as well as antidepressant action. The 5HT1A partial agonist properties of numerous drugs for psychosis are also discussed in Chapter 5 and illustrated in Figures 5-22 and 5-23, and the downstream actions of 5HT1A receptor stimulation are discussed in Chapter 4 and illustrated in Figure 4-44. The potential anxiolytic actions of buspirone could theoretically be due to 5HT1A partial agonist actions at both presynaptic and postsynaptic 5HT1A receptors (Figures 7-23 through 7-27), actions at both sites resulting in enhanced serotonergic activity in projections to the amygdala (Figure 8-17D), prefrontal cortex, striatum, and thalamus (Figure 8-18D), and thus reduce fear and worry, as well as other symptoms of both generalized anxiety disorder and major depression (Figure 8-1). SSRIs and SNRIs theoretically do the same thing (Figures 8-17D and 8-18D). Since the onset of anxiolytic action for buspirone is delayed, just as it is for drugs for depressions, this has led to the belief that 5HT1A agonists exert their therapeutic effects by virtue of adaptive neuronal events and receptor events (Figures 7-10 through 7-15 and Figures 7-23 through 7-27), rather than simply by the acute occupancy of 5HT1A receptors. In this way, the presumed mechanism of action of 5HT1A partial agonists is analogous to the use of various drugs for depression, including SSRIs and SNRIs. These actions are quite different in timing from the use of benzodiazepines for anxiety – since benzodiazepines act acutely by occupancy of benzodiazepine receptors and not with a delay due to adaptation of the receptors.
NORADRENERGIC HYPERACTIVITY IN ANXIETY Norepinephrine is another neurotransmitter with important regulatory input to the amygdala (Figure 8-19A) and to the prefrontal cortex and thalamus in CSTC circuits (Figure 8-20A). Excessive noradrenergic output from the locus coeruleus can result not only in numerous peripheral manifestations of autonomic overdrive, as discussed above and as illustrated in Figures 8-8 through 8-12, but also can trigger numerous central symptoms of anxiety and fear, such as nightmares, hyperarousal states, flashbacks, and panic attacks (Figure 8-19A). Excessive noradrenergic activity can also reduce the efficiency of information processing in the prefrontal cortex and thus in CSTC circuits, and theoretically cause worry (Figure 8-20A). Hypothetically, these symptoms may be mediated in part by excessive noradrenergic input onto α1- and β1-adrenergic postsynaptic receptors in the amygdala (Figure 8-19A) or prefrontal cortex (Figure 8-20A). Symptoms of hyperarousal like nightmares can be reduced in some patients with α1-adrenergic blockers such as prazocin (Figure 8-19B), and symptoms of fear (Figure 8-19C) and worry (Figure 8-20B) can be reduced by norepinephrine reuptake inhibitors (also called norepinephrine transporter [NET] inhibitors). The clinical effects of NET inhibitors can be confusing because symptoms of anxiety can actually be made transiently worse immediately following initiation of an SNRI or selective NET inhibitor, when noradrenergic activity is initially increased but the postsynaptic receptors have not yet adapted. However, these same NET inhibitory actions, if sustained over time, will downregulate and desensitize postsynaptic norepinephrine receptors such as β1 receptors, and hypothetically lead to the delayed reduction in symptoms of fear and worry long term (Figure 8-20B). FEAR CONDITIONING VERSUS FEAR EXTINCTION Fear conditioning is a concept as old as Pavlov’s dogs. If an aversive stimulus such as footshock is coupled with a neutral stimulus such as a bell, the animal learns to associate the two, and will develop fear when it hears a bell. In humans, fear can be “learned” during stressful experiences associated with emotional trauma, and is influenced by an individual’s genetic predisposition as well as by an individual’s prior exposure to environmental stressors that can cause stress sensitization of brain circuits (e.g., child abuse; see Chapter 6 and Figures 6-28 and 6-

33). Often, fearful situations are managed successfully and then forgotten. Some fears are crucial for survival, such as appropriately fearing dangerous situations, and thus the mechanism of learned fear, called fear conditioning, has been extremely well conserved across species, including humans. However, other fears that are “learned” and, if not “forgotten,” may hypothetically progress to anxiety disorders or a major depressive episode. This is a big problem since almost

Chapter 8: Anxiety, Trauma, and Treatment Figure 8-19 Noradrenergic hyperactivity in anxiety/fear. (A) Norepinephrine provides input not only to the amygdala but also to many regions to which the amygdala projects; thus it plays an important role in the fear response. Noradrenergic hyperactivation can lead to anxiety, panic attacks, tremors, sweating, tachycardia, hyperarousal, and nightmares. Alpha-1 and β1-adrenergic receptors may be specifically involved in these reactions. (B) Noradrenergic hyperactivity may be blocked by the administration of α1-adrenergic antagonists, which can lead to the alleviation of anxiety and other stress-related symptoms. (C) Noradrenergic hyperactivity may also be blocked by the administration of a norepinephrine transporter (NET) inhibitor, which can have the downstream effect of downregulating β1-adrenergic receptors. Reduced stimulation via β1-adrenergic receptors could therefore lead to the alleviation of anxiety and stress-related symptoms. Noradrenergic Hyperactivity in Anxiety, Fear, and Autonomic Hyperarousal Therapeutic Actions of Alpha-1 Antagonists on Nightmares and Hyperarousal Therapeutic Actions of NET Inhibitors on Anxiety, Fear, and Hyperarousal amygdala amygdala amygdala 1 receptor ß1 receptor NE NET inhibitor downregulated ß1 receptors 1 receptor NE 1 receptor ß1 receptor NE 1 blocker locus coeruleus A B locus coeruleus locus coeruleus C fear/panic attacks tremor sweating tachycardia hyperarousal nightmares fear/panic attacks tremor sweating tachycardia hyperarousal nightmares fear/panic attacks tremor sweating tachycardia hyperarousal nightmares

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Affect of Fear Hyperactive CSTC Circuits and Worry worry A Delayed Therapeutic Actions of NET Inhibitors worry B NE neuron locus coeruleus Figure 8-20 Noradrenergic hyperactivity in worry. (A) Pathological worry may be caused by overactivation of corticostriato-thalamo-cortical (CSTC) circuits. Specifically, excessive noradrenergic activity within these circuits can reduce the efficiency of information processing and theoretically cause worry. (B) Noradrenergic hyperactivity in CSTC circuits may be blocked by the administration of a norepinephrine transporter (NET) inhibitor, which can have the downstream effect of downregulating β1-adrenergic receptors. Reduced stimulation via β1-adrenergic receptors could therefore lead to the alleviation of worry. 30% of the population will develop an anxiety disorder, due in large part to stressful environments, including exposure to fearful events during normal activities in twenty-first-century society, but in particular during early life, if experiencing abuse or adversity as a child, and during war and natural disasters, and abusive relationships, as an adult. Repetition of a sensory experience associated with an earlier exposure to a fearful event, such as hearing or seeing an explosion, smelling burning rubber, seeing a picture of a wounded civilian, seeing or hearing flood waters, can trigger traumatic re-experiencing and generalized hyperarousal and fear in emotionally traumatized patients with PTSD. Panic associated with social situations will “teach” the patient to panic in social situations in social anxiety disorder. Panic randomly associated with an attack that happens to occur in a crowd, on a bridge, or in shopping centers will also trigger another panic attack when the same environment is encountered in panic disorder. These and other symptoms of anxiety disorders are all forms of learning known as fear conditioning (Figure 8-21). The amygdala is theoretically involved in “remembering” the various stimuli

associated with a given fearful situation. Hypothetically, the amygdala does this by increasing the efficiency of neurotransmission at glutamatergic synapses in the lateral amygdala as sensory input about those stimuli comes in from the thalamus or sensory cortex (Figure 8-21). This input is then relayed to the central amygdala, where fear conditioning also improves the efficiency of neurotransmission at another glutamate synapse there (Figure 8-21). Both synapses are hypothetically restructured and potentially permanent learning is embedded into this circuit by NMDA receptors, triggering long-term potentiation and synaptic plasticity so that subsequent input from the sensory cortex and thalamus is very efficiently processed to trigger the same fear response caused by the original experience, since output occurs from the central amygdala every time there is the re-experiencing of the same sensory input associated with the original fearful event (Figure 8-21; see also Figures 8-8 through 8-13). Input to the lateral amygdala is modulated by the prefrontal cortex, especially the ventromedial prefrontal cortex (VMPFC), and by the hippocampus. If the VMPFC is unable to suppress the fear response before it arrives at the level of the amygdala, fear conditioning is thought to proceed. The hippocampus hypothetically "remembers" the context of the fear conditioning, and makes sure fear is triggered when the fearful stimulus and all its associated stimuli are encountered again. Most contemporary psychopharmacological treatments for anxiety and fear act by suppressing the fear output from the amygdala (see Figure 8-17) and therefore are not cures since the fundamental neuronal learning underlying fear conditioning in these patients remains in place. On the other hand, psychotherapeutic approaches perhaps enhanced by drugs targeting the "unlearning"

Chapter 8: Anxiety, Trauma, and Treatment Figure 8-21 Fear conditioning versus fear extinction. When an individual encounters a stressful or fearful experience, the sensory input is relayed to the amygdala, where it is integrated with input from the ventromedial prefrontal cortex (VMPFC) and hippocampus, so that a fear response can be either generated or suppressed. The amygdala may "remember" stimuli associated with that experience by increasing the efficiency of glutamate neurotransmission, so that on future exposure to stimuli, a fear response is more efficiently triggered. If this is not countered by input from the VMPFC to suppress the fear response, fear conditioning proceeds. Fear conditioning is not readily reversed, but it can be inhibited through new learning. This new learning is termed fear extinction and is the progressive reduction of the response to a feared stimulus that is repeatedly presented without adverse consequences. Thus the VMPFC and hippocampus learn a new context for the feared stimulus and send input to the amygdala to suppress the fear response. The "memory" of the conditioned fear is still present, however. Fear Conditioning vs. Fear Extinction fear extinction renewal

lateral amygdala central amygdala = glutamate = GABA intercalated cell mass no fear response fear conditioning no fear response fear response!!! VMPFC hippocampus VMPFC hippocampus sensory cortex thalamus fear conditioning fear extinction

 of fear conditioning provide hope for a more long-lasting solution to symptoms of anxiety. Novel Approaches to the Treatment of Anxiety Disorders Once fear conditioning is in place, it can be very difficult to reverse. Nevertheless, there may be two ways to neutralize fear conditioning: either by facilitating a process called extinction or by blocking a process called reconsolidation. Research on extinction and reconsolidation are leading the way in order to find novel, more robust, and more long-lasting treatments for anxiety symptoms, especially in patients who do not respond to standard treatment with serotonergic,

benzodiazepine, and α2δ drug therapies or to standard psychotherapies such as exposure treatment or cognitive behavioral therapy. Preventing or minimizing “stress” – especially early life adversity in young children, and chronic stress and catastrophic stress in adults – is also under investigation but difficult to implement. Fear Extinction Fear extinction is the progressive reduction of the response to a feared stimulus, and occurs when the stimulus is repeatedly presented without any adverse consequence. When fear extinction occurs, it appears that the original fear conditioning is not really “forgotten” even though the fear response can be profoundly reduced over time by the active process of fear extinction. Rather than reversing the synaptic changes described above for fear conditioning, leading theories propose that a new form of learning with additional synaptic changes in the amygdala occurs during fear extinction. These changes hypothetically suppress symptoms of anxiety and fear by inhibiting the original learning but not by removing it (Figure 8-21). Specifically, if activation of the amygdala by the VMPFC occurs again and again without any fear being triggered, such as during exposure therapy, the hippocampus hypothetically begins to “remember” this new context in which the feared stimulus did not have any adverse consequences and fear is no longer activated (Figure 8-21). Over time, the original stimulus no longer activates fear due to this process of progressive desensitization called fear extinction. Such fear extinction hypothetically occurs when inputs from the VMPFC and hippocampus now “learn” to activate glutamatergic neurons in the lateral amygdala that synapse upon inhibitory GABAergic interneurons, located within the intercalated cell mass of the amygdala (Figure 8-21). According to this theory, such an action sets up a gate within the central amygdala, with fear output occurring if the fear-conditioning circuit predominates, and no fear output occurring if the fear-extinction circuit predominates. Modern research thus suggests that fear extinction theoretically predominates over fear conditioning when synaptic strengthening and long-term potentiation in the new circuit are able to produce an inhibitory GABAergic drive that can overcome the excitatory glutamatergic drive produced by the pre-existing fear-conditioning circuitry (Figure 8-21). When fear extinction exists simultaneously with fear conditioning, memory for both are present, but the output hypothetically depends upon which system is “stronger” and “better-remembered,” and which has the most robust synaptic efficiency. These factors will hypothetically determine which gate will open, the one with the fear response or the one that keeps the fear response in check. Unfortunately, over time, fear conditioning in experimental models and in clinical practice may have the upper hand over fear extinction. Fear extinction appears to be more labile than fear conditioning, and tends to reverse over time. Also, fear conditioning can return if the old fear is presented in a context different from the one “learned” to suppress the fear during fear extinction, a process termed “renewal.” Therapeutic Facilitation of Fear Extinction A novel treatment approach to reducing anxiety symptoms is to facilitate fear extinction with a combination of psychotherapy and drugs directed at facilitating synapse formation. This approach contrasts with how current effective anxiolytic drugs act, namely by pharmacologically suppressing the fear response (Figures 8-17 through 8-20). Among currently effective psychotherapies for anxiety used in clinical practice today, cognitive behavioral therapies that employ exposure techniques and that require the patient to confront the fear-inducing stimuli in a safe environment may come closest to facilitating fear extinction, hypothetically because when these therapies are effective, they are able to trigger the learning of fear extinction in the amygdala (Figure 8-21). Unfortunately, because the hippocampus “remembers” the context of this extinction, such therapies are often context-specific and do not always generalize once the patient is outside the safe therapeutic environment of a therapist’s office, and thus fear and worry may be “renewed” in the real world. Current psychotherapy research is investigating how contextual cues

can be used to strengthen extinction

learning so that the therapeutic learning generalizes to other environments. Current psychopharmacology research is investigating how specific drugs might also strengthen extinction learning by pharmacologically strengthening the synapses on the fear-extinction side of the amygdala gate disproportionately to the synapses on the fear-conditioned side of the amygdala gate. How could this be done? Based on successful animal experiments of extinction learning, one idea shown in Figure 8-22 is to pharmacologically boost N-methyl-D-aspartate (NMDA) receptor activation at the very time when a patient receives systematic exposure to feared stimuli during cognitive behavioral therapy sessions. The idea is that as psychotherapy progresses, learning occurs, because glutamate release is provoked in the lateral amygdala and in the intercalated cell mass at inhibitory GABA neurons by the psychotherapy. If NMDA receptors at these two glutamate synapses could be pharmacologically boosted to trigger disproportionately robust long-term potentiation and synaptic plasticity, timed to occur at the exact time this learning and therapy is taking place and thus exactly when these synapses are selectively activated, it could theoretically result in the predominance of the extinction pathway over the conditioned pathway. Animal fear extinction glial cell Glu glycine enhancing NMDA action LTP no fear response Chapter 8: Anxiety, Trauma, and Treatment studies support this possibility and early clinical studies are encouraging but not always robust or consistent, to date. In the meantime, prudent psychopharmacologists are increasingly leveraging their current anxiolytic drug portfolio with concomitant psychotherapy, since many patients already receive enhanced therapeutic benefit from this combination. Blocking Fear Conditioning and Fear Memories Blocking either consolidation or reconsolidation of fear memories is another approach to developing novel treatments for anxiety symptoms. When fear is first conditioned, that memory is said to be “consolidated” via a molecular process that some have thought was essentially permanent. Hints at the mechanism of the initial consolidation of fear conditioning come from observations that both β blockers and opioids can potentially mitigate the conditioning of the original traumatic memory, even in humans, and some studies show that these agents can potentially reduce the chances of getting PTSD after a traumatic injury (Figure 8-23). This therapeutic approach is to treat the acutely exposed patient immediately after a traumatic experience in order to block the initial fear from ever becoming conditioned or consolidated. Figure 8-22 Facilitating fear extinction with NMDA receptor activation. Strengthening of synapses involved in fear extinction could help enhance the development of fearextinction learning in the amygdala and reduce symptoms of anxiety disorders. Administration of an agent that enhances N-methyl-D-aspartate (NMDA) action while an individual is receiving exposure therapy could increase the efficiency of glutamate (Glu) neurotransmission at synapses involved in fear extinction. If this leads to long-term potentiation (LTP) and synaptic plasticity while the synapses are activated by exposure therapy, it could result in structural changes in the amygdala associated with the fear-extinction pathway and thus the predominance of the extinction pathway over the conditioned pathway. no fear response 375

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Beta Blockers and Opiates Prevent Fear Conditioning and Reconsolidation of Fear ß1 blocker VMPFC fear conditioning hippocampus opiates ß1 blocker ß1 blocker reconsolidation no fear response locus coeruleus Although, classically, emotional memories that have already been “fear conditioned” were thought to last forever, recent animal experiments show that emotional memories can in fact be weakened or even erased at the time they are re-experienced. Current theories now suggest that at the time emotional memories are re-

experienced, they are in a labile state capable of being modified, and then, once the re-experiencing of the emotion and any modification of it is complete, the memory is restored or “reconsolidated” with those modifications. Reconsolidation is the state in which reactivation of a consolidated fear memory makes it labile, and requires protein synthesis to keep the memory intact. If emotional memories consolidated as fear conditioning are not permanent, as animal Figure 8-23 Blocking fear conditioning and reconsolidation. When fear is first conditioned, the memory is said to be “consolidated” via a molecular process that once was thought to be permanent. However, there is some research to suggest that administration of either β-adrenergic blockers or opiates can potentially mitigate the conditioning of the original traumatic memory. Furthermore, research also now shows that even when emotional memories have been consolidated as fear conditioning, they can change when they are retrieved. Reconsolidation is the state in which reactivation of a consolidated fear memory makes it labile. This requires protein synthesis to keep the memory intact and, like fear conditioning, may also be disrupted by β blockers. traumatic experience traumatic experience retrieved experiments suggest, and can change when they are retrieved, the idea is to use both psychotherapeutic and psychopharmacological approaches to block reconsolidation of the fear memory. Blocking reconsolidation would hypothetically allow the patient to “forget” their emotional memory. Early studies of β blockers suggest that they may also disrupt reconsolidation of fear memories as well as formation of fear conditioning (Figure 8-23). More recently, hallucinogens, dissociatives, and entactogens such as psilocybin, MDMA (3,4-methylenedioxymethamphetamine), and ketamine have been employed in an attempt to block reconsolidation of activated memories during psychotherapy sessions. These are discussed in more detail in Chapter 13 on substance abuse; psilocybin and MDMA are discussed

briefly in Chapter 7 and illustrated in Figures 7-87 and 7-88. Ketamine is more extensively discussed in Chapter 7 as well. Future research is trying to determine how to use psychotherapy to provoke emotional memories and reactivate them by producing a state where a pharmacological agent such as a hallucinogen producing a dissociative state, including ketamine as well as psilocybin or MDMA, could be administered to disrupt reconsolidation of these emotional memories and thereby relieve symptoms of anxiety, trauma, re-experiencing and other emotional memories of PTSD and anxiety disorders, and existential distress in terminally ill patients. These are early days in terms of applying this concept in clinical settings, but this notion supports the growing idea that psychotherapy and psychopharmacology can be synergistic. Much more needs to be learned as to how to exploit this theoretical synergy. TREATMENTS FOR ANXIETY DISORDER SUBTYPES Generalized Anxiety Disorder Psychopharmacological treatments for generalized anxiety disorder overlap greatly with those for other anxiety disorders and depression and include SSRIs, SNRIs, benzodiazepines, buspirone, and α2δ ligands such as pregabalin and gabapentin. While benzodiazepines should not be prescribed to a patient with generalized anxiety disorder who is abusing other substances, particularly alcohol, benzodiazepines can be useful in patients who are not substance abusers for short terms when initiating an SSRI or SNRI, since these serotonergic agents are often activating, difficult to tolerate early in dosing, and have a delayed onset of action. In other patients, benzodiazepines can be useful to “top up” an SSRI or SNRI for patients who have experienced only partial relief of symptoms and have stabilized on SSRI/SNRI therapy. Benzodiazepines can also be useful for occasional intermittent use when symptoms surge and sudden relief is needed. Alpha-2delta ligands are a good alternative to benzodiazepines in some patients. These ligands are approved for the treatment of anxiety in Europe and other countries but

not in the US, yet can be useful “off-label” as augmenting agents. Other “off-label” treatments for anxiety can include mirtazapine, trazodone, vilazodone, tricyclic antidepressants, or even sedating antihistamines such as hydroxyzine. Chapter 8: Anxiety, Trauma, and Treatment Panic Disorder Panic attacks occur in many conditions, not just panic disorder, and panic disorder is frequently comorbid with the other anxiety disorders and with major depression. It is thus not surprising that contemporary treatments for panic disorder overlap significantly with those for the other anxiety disorders and with those for major depression. Treatments include SSRIs and SNRIs, as well as benzodiazepines, and α2δ ligands. “Off-label” treatments of panic attacks in anxiety disorders can also include mirtazapine and trazodone. The monoamine oxidase inhibitors (MAOIs), discussed in Chapter 7, are much neglected in psychopharmacology in general and for the treatment of treatment-resistant panic disorder in particular. However, MAOIs can have powerful efficacy in panic and should be considered when other agents fail. Cognitive behavioral psychotherapy is both an alternative or an augmentation to psychopharmacological approaches, and can help modify cognitive distortions, and, through exposure, diminish phobic avoidance behaviors. Social Anxiety Disorder The treatment options for this anxiety disorder are very similar to those for panic disorder with a few noteworthy differences. The SSRIs and SNRIs and α2δ ligands are certainly useful treatments, but the utility of benzodiazepine is not as widely accepted as it might be for generalized anxiety disorder and panic disorder. There is also less evidence for the utility of older drugs for depression for use in social anxiety disorder. Beta blockers, sometimes with benzodiazepines, can be useful for some patients with very discrete types of social anxiety, such as performance anxiety. One drug that is (unfortunately) quite effective but obviously should not be used is alcohol for the treatment of social anxiety symptoms. Many patients of course are aware of this and abuse alcohol before they seek safer and more effective treatment. Cognitive behavioral psychotherapy can be a powerful intervention, sometimes better than drugs for certain patients, and often helpful in combination with drugs. PTSD Although some treatments such as certain SSRIs are approved for PTSD, psychopharmacological treatments for PTSD are not as effective as these same treatments are in anxiety disorders. Also, PTSD is so highly comorbid that many of the psychopharmacological treatments are more effectively aimed at comorbidities such as 377

 depression, insomnia, substance abuse, and pain, than at core symptoms of PTSD. SSRIs often leave the patient with residual symptoms, including sleep problems. Thus, most patients with PTSD do not take monotherapy. Benzodiazepines are to be used with caution, not only because of limited evidence from clinical trials for efficacy in PTSD, but also because many PTSD patients abuse alcohol and other substances. A unique treatment for PTSD is the administration of α1 antagonists at night to prevent nightmares. Much more effective medication treatments for PTSD are greatly needed. Much of the advance in treatment of PTSD has been in using drugs to treat comorbidities and psychotherapies to treat core symptoms. Exposure therapy is perhaps most effective among psychotherapies, but many forms of cognitive behavioral therapy are being investigated and used in clinical practice, depending upon the training of the therapist and the specific needs of the individual. Use of techniques to block reconsolidation of emotional memories with the combination of psychotherapy and drugs (especially MDMA) are in testing now for PTSD. Brexpiprazole, discussed in Chapter 5 as a drug for psychosis, is in testing along with the SSRI sertraline for PTSD, with promising initial findings. SUMMARY Anxiety/trauma disorders have core features of fear and worry that cut across the entire spectrum of anxiety disorder subtypes, from generalized anxiety disorder to panic disorder, social anxiety disorder, and posttraumatic stress disorder. The amygdala hypothetically plays a central role in the fear response in these conditions, and cortico-striato-thalamo-cortical (CSTC) circuits are thought to

play a key role in mediating the symptom of worry. Numerous neurotransmitters are involved in regulating the circuits that underlie the anxiety disorders. Serotonin, norepinephrine, α2δ ligands and GABA are all key modulators of the hypothetical fear and worry circuits. Known effective drug treatments all target these neurotransmitters. The concept of opposing actions of fear conditioning versus fear extinction within amygdala circuits hypothetically is linked to the production and maintenance of symptoms in anxiety disorder and provides a substrate for potential novel therapeutics combining psychotherapy and drugs. The concept of disruption of the reconsolidation of fear memories is undergoing testing at this time as a novel therapeutic approach to anxiety symptoms.

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