This chapter will provide a brief overview of anxiety disorders and their treatments. Included are descriptions of how the anxiety disorder subtypes overlap with each other and with major depressive disorder. Clinical descriptions and formal criteria for how to diagnose anxiety disorder subtypes are mentioned only in passing. The reader should consult standard reference sources for this material. The discussion here will emphasize how discoveries about the functioning of various brain circuits and neurotransmitters—especially those centered on the amygdala—affect our understanding of fear and worry, which cut across the entire spectrum of anxiety disorders.

The goal of this chapter is to acquaint the reader with ideas about the clinical and biological aspects of anxiety disorders in order to clarify the mechanisms of action of the various treatments for these disorders as they are discussed along the way. Many of these treatments are extensively discussed in previous chapters. For details of mechanisms of anxiolytic agents used also for the treatment of depression (i.e., certain antidepressants),
I Overlap of MDD and Anxiety Disorders

• depressed • anxiety mood Interest! ~ worry panic attacks
..• pleasure gUilt! ..•
worthlessness phobic avoidance
sUlcldality appetite/ Irritability compulsionsweight muscletension
major depressive disorder

FIGURE 14-1 Overlap of MDD 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 "MDD" puzzle on the left). For example, fatigue, sleep difficulties, and problems concentrating are common to both types of disorders.

the reader is referred to Chapter 12; for those anxiolytic agents used also as mood stabilizers for the treatment of bipolar disorder (i.e., certain anticonvulsants), the reader is referred to Chapter 13; and for those anxiolytics used as antipsychotics, the place to look is Chapter 10. The discussion in this chapter is at the conceptual level, and not at the pragmatic level. The reader should consult standard drug handbooks (such as Essential Psychopharmacology: 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 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 and constitutes a psychiatric disorder. The idea of anxiety as a psychiatric disorder is evolving rapidly. It is characterized by the concept of core symptoms of excessive fear and worry (symptoms at the center of anxiety disorders in Figure 14-1) 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 14-1).

Anxiety disorders have considerable symptom overlap with major depression (see those symptoms surrounding core features shown in Figure 14-1), particularly sleep disturbance, problems concentrating, fatigue, and psychomotor/arousal symptoms. Each anxiety disorder also has a great deal of symptom overlap with other anxiety disorders (Figures 14-2 through 14-6). 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 14-2 through 14-6). Finally, anxiety disorders are frequently comorbid with many other conditions such as substance abuse, attention deficit
FIGURE 14-2 Generalized anxiety disorder (GAD). The symptoms typically associated with GAD 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.

FIGURE 14-3 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.
FIGURE 14-4 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.

FIGURE 14-5 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 reexperienced 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.
FIGURE 14-6 Obsessive compulsive disorder (OCD). Symptoms of OCD, shown here, include the core symptom of anxiety, which triggers obsessions and compulsions in attempts to reduce that worry as well as the obsessions themselves, which can be seen as a type of worry. Compulsions are a key associated feature.

FIGURE 14-7 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.

hyperactivity disorder, bipolar disorder, pain disorders, sleep disorders, and more, just as in major depression (discussed in Chapter 12 and illustrated in Figure 12-127) and bipolar disorder (discussed in Chapter 13 and illustrated in Figure 13-42).

What, therefore, 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 (Figure 14-7), 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 14-1) and then to recede...
into subsyndromal levels only to reappear again as the original anxiety disorder, a different anxiety disorder (Figures 14-2 through 14-6), or major depression (Figure 14-1). If anxiety disorders all share core symptoms of fear and worry (Figure 14-7) and, as discussed 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: What is the difference between one anxiety disorder and another? Also, one could ask: What is the difference between major depression and anxiety disorders? Are all these entities really different disorders or are they just 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 (anxiety/fear and worry), there is a great deal of overlap with the other symptoms considered diagnostic for both a major depressive episode and several different anxiety disorders (Figure 14-1). These overlapping symptoms include problems with sleep, concentration, and fatigue as well as psychomotor/arousal symptoms (Figure 14-1). 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 disorder (Figure 14-1) or one anxiety disorder into another (Figures 14-2 through 14-6).

From a therapeutic point of view, it may matter little what the specific diagnosis is across this spectrum of disorders (Figures 14-1 through 14-6). 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 with full-criteria anxiety symptoms. Although it can be useful to make specific diagnoses for following patients over time and for documenting the evolution of symptoms, the emphasis from a psychopharmacological point of view is increasingly to take a symptom-based therapeutic strategy to patients with any of these disorders. 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 14-2 through 14-6) and then matching these symptoms to hypothetically malfunctioning brain circuits regulated by specific neurotransmitters in order to rationally select and combine psychopharmacological treatments to eliminate all symptoms and get the patient to remission.

Discussion of this strategy for treating the symptoms of a major depressive episode to attain remission is provided in Chapter 12 and illustrated in Figures 12-120 to 12-126. Specific discussion of how to approach the overlapping symptoms of problems with sleep, concentration, and fatigue are illustrated in Figures 12-121 to 12-123.

**Overlapping symptoms of anxiety disorder subtypes**

Although there are different diagnostic criteria for different anxiety disorders (Figures 14-2 through 14-6), they can all be considered to have overlapping symptoms of anxiety/fear coupled with worry (Figure 14-7). Remarkable progress has been made in understanding the circuitry underlying the core symptom of anxiety/fear (Figure 14-7) based on an explosion of neurobiological research on the amygdala (Figures 14-8 through 14-42). The links between the amygdala, fear circuits, and treatments for the symptom of anxiety/fear across the spectrum of anxiety disorders are discussed throughout the rest of this chapter.

Worry is the second core symptom shared across the spectrum of anxiety disorders (Figure 14-8). This symptom is hypothetically linked to the functioning of cortico-striatal-
Associate Symptoms of Anxiety With Brain Regions and Circuits That Regulate Them

**FIGURE 14-8 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-striatal-thalamic-cortical (CSTC) loop. These circuits may be involved in all anxiety disorders, with the different phenotypes reflecting not unique circuitry but rather divergent malfunctioning within those circuits.

**FIGURE 14-9 Amygdala.** The amygdala, which plays a central role in the experience of anxiety and fear, has reciprocal connections with a wide range of other brain regions. These connections allow the amygdala to integrate both sensory and cognitive information and then use that information to trigger (or not) a fear response.

thalamo-cortical (CSTC) loops. CSTC loops were introduced in Chapter 7 and are illustrated in Figures 7-16 through 7-21. The links between the CSTC circuits, “worry and obsession loops,” and treatments for the symptom of worry across the spectrum of anxiety disorders are discussed later in this chapter (see also Figures 14-43 through 14-45). We shall see that what differentiates one anxiety disorder from another may not be the anatomical localization or neurotransmitters regulating fear and worry (Figure 14-7 and Figure 14-8) but rather the specific nature of malfunctioning within these same circuits in various anxiety disorders.
That is, in generalized anxiety disorder, malfunctioning in the amygdala and CSTC loops may be persistent and unremitting yet not severe (Figure 14-2), whereas malfunctioning may be intermittent but catastrophic in an unexpected manner for panic disorder (Figure 14-3) or in an expected manner for social anxiety (Figure 14-4). Circuit malfunctioning may be traumatic in origin in posttraumatic stress disorder (PTSD) (Figure 14-5) or trapped in a redundant, repetitive loop for obsessive compulsive disorder (OCD) (Figure 14-6).
Endocrine Output of Fear

FIGURE 14-12 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.

Breathing Output

FIGURE 14-13 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.

The amygdala and the neurobiology of fear

The amygdala, an almond-shaped brain center located near the hippocampus (see Figure 9-63), has important anatomical connections that allow it to integrate sensory and cognitive information and then to determine whether there will be a fear response (see Figures 9-64 and 9-65 as well as Figures 7-12, 7-13, and 7-19 through 7-20). Figures 14-9 through 14-15 illustrate how the amygdala's connections relate to the signs and symptoms associated with the 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,
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.

Reexperiencing

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 reexperiencing and is a particular feature of posttraumatic stress disorder.

namely the orbitofrontal cortex and the anterior cingulate cortex (Figure 14-10). However, fear is not just a feeling. The fear response can also include motor responses. Depending on 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 14-11).

There are also endocrine reactions that accompany fear, in part due to connections between the amygdala and the hypothalamus, causing changes in the hypothalamic-pituitary-adrenal (HPA) axis and thus of cortisol levels. A quick boost of cortisol may enhance survival when a person is encountering a real but short-term 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 14-12). Breathing can also change during a fear response, regulated in part by the connections between amygdala and the parabrachial nucleus in the brainstem.
Associate Symptoms With Brain Regions, Circuits, and Neurotransmitters That Regulate Them

FIGURE 14-16 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), gamma-aminobutyric acid (GABA), glutamate, corticotrophin releasing factor (CRF), and norepinephrine (NE), among others. In addition, voltage-gated ion channels are involved in neurotransmission within these circuits.

(Figure 14-13). An adaptive response to fear is to accelerate respiratory rate in the course of a fight/flight reaction to enhance survival; in excess, however, this can lead to unwanted symptoms of shortness of breath, exacerbation of asthma, or a false sense of being smothered (Figure 14-13) – all of which are 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 – such as increased pulse and blood pressure for fight/flight reactions and survival during real threats – from the cardiovascular system. These autonomic and cardiovascular responses are mediated by connections between the amygdala and the locus coeruleus, home of the noradrenergic cell bodies (Figure 14-14) (noradrenergic neurons are discussed in Chapters 7 and 11 and noradrenergic pathways are illustrated in Figure 7-9). When autonomic responses are repetitive – that is, when they are inappropriately or chronically triggered as part of an anxiety disorder – this can eventually lead to increases in atherosclerosis, cardiac ischemia, hypertension, myocardial infarction, and even sudden death (Figure 14-15). “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 14-15), especially in conditions such as posttraumatic stress disorder.

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 14-16). Some of the key neurotransmitters acting at the amygdala are shown in Figure 14-16, although the exact anatomical connections within the amygdala and the specific receptor subtypes for these various circuits are still being clarified. What is known about these connections is that several neurotransmitters are involved in the production of symptoms of anxiety at the level of the amygdala and that numerous anxiolytic drugs have actions on these specific neurotransmitter systems to relieve the symptoms of anxiety and fear (Figure 14-16).
GABA, anxiety, and benzodiazepines

GABA is one of the key neurotransmitters involved in anxiety and in the anxiolytic action of many drugs used to treat the spectrum of anxiety disorders. GABA is the principal inhibitory neurotransmitter in the brain and normally serves an important regulatory role in reducing the activity of many neurons, including those in the amygdala and in the CSTC loops. Benzodiazepines, perhaps the best-known and most widely used anxiolytics, act by enhancing GABA actions at the level of the amygdala and the prefrontal cortex within CSTC loops to relieve anxiety. To understand how GABA regulates brain circuits in anxiety and how benzodiazepines exert their anxiolytic actions, it is important to understand the GABA neurotransmitter system, including how GABA is synthesized, how its action is terminated at the synapse, and especially the properties of GABA receptors (Figures 14-17 through 14-25).

Specifically, GABA is produced, or synthesized, from the amino acid glutamate (glutamic acid) via the actions of the enzyme glutamic acid decarboxylase (GAD) (Figure 14-17). Once formed in presynaptic neurons, GABA is transported into synaptic vesicles by vesicular inhibitory amino acid transporters (VIAATs), where GABA is stored until it is released into the synapse during inhibitory neurotransmission (Figure 14-17). GABA's synaptic actions are terminated by the presynaptic GABA transporter (GAT), also known as the GABA reuptake pump (Figure 14-18), analogous to similar transporters for other
FIGURE 14-18 Gamma-aminobutyric acid (GABA) action is terminated. GABA's action can be terminated through multiple mechanisms. GABA can be transported out of the synaptic cleft and back into the presynaptic neuron via the GABA transporter (GAT), where it may be repackaged for future use. Alternatively, once GABA has been transported back into the cell, it may be converted into an inactive substance via the enzyme GABA transaminase (GABA-T).

neurotransmitters discussed throughout this text. VIAATs and GATs are introduced in Chapter 4 and illustrated in Figure 4-10. GABA's action can also be terminated by the enzyme GABA transaminase (GABA-T), which converts GABA into an inactive substance (Figure 14-18).

Classification of numerous GABA receptor subtypes has proceeded at a rapid pace. An understanding of the properties of GABA receptor subtypes is the key to grasping the role of GABA in anxiety and the mechanism of action of benzodiazepine anxiolytics. There are three major types of GABA receptors and numerous subtypes of GABA receptors. The major types are GABA-A, GABA-B and GABA-C receptors (Figure 14-19). GABA-A receptors and GABA-C receptors are both ligand-gated ion channels. This class of receptor, also known as ionotropic receptors and as ion channel-linked receptors, is discussed in Chapter 5 and illustrated in Figures 5-2 through 5-25. Both GABA-A receptors and GABA-C receptors are part of a macromolecular complex that forms an inhibitory chloride channel (Figure 14-20). As will be explained here in detail, various subtypes of GABA-A receptors are targets of benzodiazepines, barbiturates, and/or alcohol (Figure 14-20) and are involved with either tonic or phasic inhibitory neurotransmission at GABA synapses.
GABA Receptors

FIGURE 14-19 Gamma-aminobutyric acid (GABA) receptors. Shown here are receptors for GABA that regulate its neurotransmission. These include the GABA transporter (GAT) as well as three major types of postsynaptic GABA receptors: GABA-A, GABA-B, and GABA-C. GABA-A and GABA-C receptors are ligand-gated ion channels; they are part of a macromolecular complex that forms an inhibitory chloride channel. GABA-B receptors are G protein-linked receptors that may be coupled with calcium or potassium channels.

GABA-A receptor subtypes

Given the critical roles of various subtypes of GABA-A receptors in mediating inhibitory neurotransmission and as targets of the anxiolytic benzodiazepines, this class of receptors will be discussed in further detail. The molecular structure of GABA-A receptors is shown in...
Structure of GABA-A Receptors

A

four transmembrane regions
extracellular amino acid chains

transmembrane region

cytoplasmic loop

five substructures form the receptor complex
the chloride channel is at the center

B

Major Subtypes of GABA-A Receptors

GABA binding site
BZ binding site
GABA binding site
BZ binding site
GABA binding site
BZ binding site
GABA binding site
BZ binding site

α(1-6) β(1-3)
γ1
δ, ε, θ, or ρ

-α1
-α2, α3
-α4, α6, γ1
-α4, α6, γ1

sedative
phasic inhibition
-anticonvulsant
phasic inhibition
-tonic inhibition
-extrasynaptic

FIGURE 14-20A, B, and C Gamma-aminobutyric acid-A (GABA-A) receptors. (A) Shown here are the four transmembrane regions that make up one subunit of a GABA-A receptor. (B) There are five copies of these subunits in a fully constituted GABA-A receptor, at the center of which is a chloride channel. (C) Different types of subunits (also called isoforms or subtypes) can combine to form a GABA-A receptor. These include six different alpha isoforms, three different beta isoforms, three different gamma isoforms, delta, epsilon, pi, theta, and three different rho isoforms. The ultimate type and function of each GABA-A receptor subtype will depend on which subunits it contains. Benzodiazepine-sensitive GABA-A receptors (middle two) contain gamma and alpha (1 through 3) subunits and mediate phasic inhibition triggered by peak concentrations of synaptically released GABA. Benzodiazepine-sensitive GABA-A receptors containing alpha 1 subunits are involved in sleep (second from left), while those that contain alpha 2 and/or alpha 3 subunits are involved in anxiety (second from right). GABA-A receptors containing alpha 4, alpha 6, gamma 1, or delta subunits (far right) are benzodiazepine-insensitive, are located extrasynaptically, and regulate tonic inhibition.
Two Types of GABA-A Mediated Inhibition

Benzodiazepine-sensitive GABA-A receptors (those that contain gamma and alpha 1 through alpha 3 subunits) are postsynaptic receptors that mediate phasic inhibition, which occurs in bursts triggered by peak concentrations of synaptically released GABA. Benzodiazepine-insensitive GABA-A receptors (those containing alpha 4, alpha 6, gamma 1, or delta subunits) are extrasynaptic and capture GABA that diffuses away from the synapse as well as neurosteroids that are synthesized and released by glia. These receptors mediate inhibition that is tonic (i.e., mediated by ambient levels of extracellular GABA that has escaped from the synapse).

Figure 14-20. Each subunit of a GABA-A receptor has four transmembrane regions (Figure 14-20A). When five subunits cluster together, they form an intact GABA-A receptor with a chloride channel in the center (Figure 14-20B). This molecular structure of ligand-gated ion channels is introduced in Chapter 5 and illustrated in Figures 5-3 and 5-4.

There are many different subtypes of GABA-A receptors, depending on which subunits are present (Figure 14-20C). Subunits of GABA-A receptors are sometimes also called isoforms and include alpha (with six isoforms, alpha 1 to 6), beta (with three isoforms, beta 1 to 3), gamma (with three isoforms, gamma 1 to 3), delta, epsilon, pi, theta, and rho (with three isoforms, rho 1 to 3) (Figure 14-20C). Important for this discussion is the fact that, depending on which subunits are present, the functions of a GABA-A receptor can vary significantly.
**Benzodiazepine-insensitive**

GABA-A receptors are those with alpha 4, alpha 6, gamma 1, or delta subunits (Figure 14-20C). GABA-A receptors with a delta subunit rather than a gamma subunit plus either alpha 4 or alpha 6 subunits do not bind to benzodiazepines. Such GABA-A receptors do bind to other modulators, namely the naturally occurring neurosteroids, as well as to alcohol and to some general anesthetics (Figure 14-20C). The binding site for these non-benzodiazepine modulators is located between the alpha and the delta subunits, one site per receptor complex (Figure 14-20C). Two molecules of GABA bind per receptor complex at sites located between the alpha and the beta subunits, sometimes referred to as the GABA agonist site (Figure 14-20C). Since the site for the modulators is in a different location from the agonist sites for GABA, the modulatory site is often called allosteric (literally “other site”), and the agents that bind there, allosteric modulators.

Benzodiazepine-insensitive GABA-A receptor subtypes (with delta subunits and alpha 4 or 6 subunits) are located extrasynaptically, where they capture not only GABA that diffuses away from the synapse but also neurosteroids synthesized and released by glia (Figure 14-21). Extrasynaptic, benzodiazepine-insensitive GABA-A receptors are thought to mediate a type of inhibition at the postsynaptic neuron that is tonic, in contrast to the phasic type of inhibition mediated by postsynaptic benzodiazepine-sensitive GABA-A receptors (Figure 14-21). Thus tonic inhibition may be regulated by the ambient levels of extracellular GABA molecules that have escaped presynaptic reuptake and enzymatic destruction. Tonic inhibition is thought to set the overall tone and excitability of the postsynaptic neuron and to be important for certain regulatory events, such as the frequency of neuronal discharge in response to excitatory inputs.

Since the GABA-A receptors that modulate this action are not sensitive to benzodiazepines, they are not likely to be involved in the anxiolytic actions of benzodiazepines in various anxiety disorders. However, novel hypnotics as well as anesthetics have targeted these extrasynaptic benzodiazepine-insensitive GABA-A receptors, and it is possible that novel synthetic neurosteroids that also target benzodiazepine-insensitive GABA-A receptor subtypes could some day become novel anxiolytics. Indeed, anxiety itself may in part be dependent on having the right amount of tonic inhibition in key anatomic areas such as the amygdala and cortical areas of CSTC loops. Furthermore, naturally occurring neurosteroids may be important in setting that inhibitory tone in critical brain areas. If this tone becomes dysregulated, it is possible that abnormal neuronal excitability could become a factor in the development of various anxiety disorders.

**Benzodiazepine-sensitive**

GABA-A receptors have several structural and functional features that make them distinct from benzodiazepine-insensitive GABA-A receptors. In contrast to benzodiazepine-insensitive GABA-A receptors, for a GABA-A receptor to be sensitive to benzodiazepines and thus to be a target for benzodiazepine anxiolytics, there must be two beta units plus a gamma unit of either the gamma 2 or gamma 3 subtype, plus two alpha units of either the alpha 1, alpha 2, or alpha 3 subtype (Figure 14-20C). Benzodiazepines appear to bind to the region of the receptor between the gamma 2/3 subunit and the alpha 1/2/3 subunit, one benzodiazepine molecule per receptor complex (Figure 14-20C). GABA itself binds with two molecules of GABA per receptor complex to the GABA agonist sites in the regions of the receptor between the alpha and the beta units (Figure 14-20C).

Benzodiazepine-sensitive GABA-A receptor subtypes (with gamma subunits and alpha 1/2/3 subunits) are thought to be postsynaptic in location and to mediate a type of
inhibition at the postsynaptic neuron that is phasic, occurring in bursts of inhibition triggered by peak concentrations of synaptically released GABA (Figure 14-21). Theoretically, benzodiazepines acting at these receptors, particularly the alpha 2/3 subtypes clustered at postsynaptic GABA sites, should exert an anxiolytic effect due to enhancement of phasic postsynaptic inhibition. If this action occurs at overly active output neurons in the amygdala or in CSTC loops, it would theoretically cause anxiolytic actions, with a reduction both of fear and worry.

Not all benzodiazepine-sensitive GABA-A receptors are the same. Notably, those benzodiazepine-sensitive GABA-A receptors with alpha 1 subunits may be most important for regulating sleep and are the presumed targets of numerous sedative hypnotic agents, including both benzodiazepine and nonbenzodiazepine positive allosteric modulators of the GABA-A receptor (Figure 14-20C). The alpha 1 subtype of GABA-A receptor and the drugs that bind to it are discussed further in Chapter 16, on sleep. Some of these agents are selective only for the alpha 1 subtype of GABA-A receptor.

On the other hand, benzodiazepine-sensitive GABA-A receptors with alpha 2 (and/or alpha 3) subunits may be most important for regulating anxiety and are the presumed targets of the anxiolytic benzodiazepines (Figure 14-20C). However, currently available benzodiazepines are nonselective for GABA-A receptors with different alpha subunits. Thus, there is an ongoing search for selective alpha 2/3 agents that could be utilized to treat anxiety disorders in man. Such agents would theoretically be anxiolytic without being sedating. Partial agonists selective for alpha 2/3 subunits of benzodiazepine sensitive GABA-A receptors hypothetically would cause less euphoria, be less reinforcing and thus less abusable, cause less dependence, and cause fewer problems in withdrawal. Such agents are being investigated but have not yet been introduced into clinical practice.

The concept of partial agonists for ligand-gated ion channels was introduced in Chapter 5 and is illustrated in Figures 5-9 through 5-15. Abnormal expression of gamma 2, alpha 2 or delta subunits is associated with different types of epilepsy. Receptor subtype expression can change in response to chronic benzodiazepine administration and withdrawal and could theoretically be altered in patients with various anxiety disorder subtypes.

Benzodiazepines as positive allosteric modulators (PAMs)

Since the benzodiazepine-sensitive GABA-A receptor complex is regulated not only by GABA itself but also by benzodiazepines at a highly specific allosteric modulatory binding site (Figure 14-22), this has led to the notion that there may be an “endogenous” or naturally occurring benzodiazepine synthesized in the brain (the brain’s own Xanax!). However, the identity of any such substance remains elusive. Furthermore, it is now known that synthetic drugs that do not have a benzodiazepine structure also bind to the benzodiazepine receptor. These developments have led to endless confusion with terminology! Thus, many experts now call the benzodiazepine site the GABA-A allosteric modulatory site and anything that binds to this site, including benzodiazepines, an allosteric modulator.

Allosteric modulation is known to occur over a broad spectrum, from positive allosteric modulation (PAM) to neutral antagonism to negative allosteric modulation (NAM). The concepts of PAMs and NAMs and the agonist spectrum are introduced in Chapter 5 and illustrated in Figure 5-21 through Figure 5-23. These ideas are further developed in Figures 14-22 through 14-24 as applied to the modulation of GABA-A receptors by benzodiazepine anxiolytics.

Acting alone, GABA can increase the frequency of opening of the chloride channel, but only to a limited extent (compare Figures 14-22A and 14-22B). The combination of
FIGURE 14-22A, B, C, and D Positive allosteric modulation of GABA-A receptors. (A) Benzodiazepine-sensitive GABA-A receptors, like the one shown here, consist of five subunits with a central chloride channel and have binding sites not only for GABA but also for positive allosteric modulators (e.g., benzodiazepines). (B) When GABA binds to its sites on the GABA-A receptor, it increases the frequency of opening of the chloride channel and thus allows more chloride to pass through. (C) When a positive allosteric modulator such as a benzodiazepine binds to the GABA-A receptor in the absence of GABA, it has no effect on the chloride channel. (D) When a positive allosteric modulator such as a benzodiazepine binds to the GABA-A receptor in the presence of GABA, it causes the channel to open even more frequently than when GABA alone is present.
T = GABA

• = benzodiazepine

FIGURE 14-23 Flumazenil. The benzodiazepine receptor antagonist flumazenil is able to reverse a full agonist benzodiazepine acting at its site on the GABA-A receptor. This may be helpful in reversing the sedative effects of full agonist benzodiazepines when administered for anesthetic purposes or when taken in overdose by a patient.

GABA with benzodiazepines is thought to increase the frequency of opening of inhibitory chloride channels but not to increase the conductance of chloride across individual chloride channels or to increase the duration of channel opening. The end result is more inhibition. More inhibition supposedly yields more anxiolytic action. How does this happen?

The answer is that benzodiazepines act as agonists at the allosteric modulatory site of GABA binding. They are positive allosteric modulators, or PAMs, but have no activity on their own. Thus, when benzodiazepines bind to the allosteric modulatory site, they have no activity when GABA is not simultaneously binding to its agonist sites (compare Figures 14-22A and 14-22C).

So how do benzodiazepines act as PAMs? This can occur only when GABA is binding to its agonist sites. The combination of benzodiazepines at the allosteric site plus GABA at its agonist sites increases the frequency of opening of the chloride channel to an extent not possible with GABA alone (compare Figures 14-22B and 14-22D).

The agonist spectrum and a hypothetical shift in the “set point” for GABA-A allosteric modulatory sites in anxiety disorders

Agonist actions of anxiolytic benzodiazepine PAMs can be reversed by the benzodiazepine antagonist known as flumazenil (Figure 14-23). Flumazenil does little by itself, since it is mostly a "silent" antagonist, but it will reverse the positive allosteric modulation of
Benzodiazepines and is used clinically to reverse sedation when benzodiazepines are taken in overdose or given as adjuncts to anesthesia.

Agents that act as inverse agonists at the GABA-A allosteric modulatory site have also been synthesized (Figure 14-24). These agents have the opposite action of benzodiazepines, and are thus negative allosteric modulators (NAMs), and cause anxiety. Members of the agonist spectrum — including agonists, silent antagonists, and inverse agonists — are discussed in greater detail in Chapter 5 and are illustrated in Figures 5-9 through 5-23.

One theory for what goes wrong in an anxiety disorder is that the “set point” for GABA-A allosteric modulatory sites is switched, either due to abnormal regulation of these sites or chronic benzodiazepine treatment, such that the entire agonist spectrum shifts (Figure 14-25). According to this theory, allosteric sites on GABA-A receptors can detect benzodiazepines, but only as partial agonists rather than full agonists; thus they have weakened efficacy for anxiety. This notion is supported by the fact that the antagonist flumazenil is “silent” and has no effects in unmedicated normal controls but can induce mild anxiety in unmedicated patients with panic disorder. This observation is consistent with a shift in receptor set point of the agonist spectrum, such that abnormal receptors in the anxiety patient now detect an antagonist as an inverse agonist and respond with the production of anxiety rather than with a neutral response. Neuroimaging research is now exploring the possibility that GABA-A receptors have abnormal regulation of their allosteric modulatory sites in a number of anxiety disorders.

Benzodiazepines as anxiolytics

A simplified notion of how benzodiazepine anxiolytics might modulate excessive output from the amygdala during fear responses in anxiety disorders is shown in Figure 14-25. Excessive amygdala activity is theoretically reduced by enhancing the phasic inhibitory actions of benzodiazepines at postsynaptic GABA-A receptors within the amygdala to blunt fear-associated outputs (shown in Figures 14-10 through 14-15).

Novel GABA anxiolytics

Ideas about how novel anxiolytics could target the GABA neurotransmitter system are shown in Figure 14-26. We have already mentioned partial agonists selective for alpha 2/3 subtypes of benzodiazepine-selective postsynaptic GABA-A receptors, shown here as well. In addition, it is possible that positive modulation of GABA-B receptors could provide an anxiolytic action. Preliminary results with the anticonvulsant tiagabine, which blocks the presynaptic transporter for GABA (GAT1), already suggest that enhancing the synaptic availability of GABA via this mechanism may provide anxiolytic effects. Finally, there are agents, including some known anticonvulsants, that enhance GABA action either by reducing its enzymatic destruction by GABA transaminase or by enhancing the release of GABA. These may prove to be useful as anxiolytics (Figure 14-26).

Serotonin, stress, and anxiety

Since the symptoms, circuits, and neurotransmitters linked to anxiety disorders overlap extensively with those for major depressive disorder (Figure 14-1), it is not surprising that drugs developed as antidepressants have proven to be effective treatments for anxiety disorders (Figure 14-27). Indeed, the leading treatments for anxiety disorders today are increasingly drugs originally developed as antidepressants.

Serotonin is a key neurotransmitter that innervates the amygdala, and it is known that antidepressants that can increase serotonin output by blocking the serotonin transporter
(SERT) are also effective in reducing symptoms of anxiety and fear in every one of the five anxiety disorders illustrated in Figures 14-2 through 14-6, namely, GAD, panic disorder, social anxiety disorder, PTSD, and OCD. Such agents include the well known SSRIs (serotonin selective reuptake inhibitors; discussed in Chapter 12; their mechanism of action is illustrated in Figures 12-17 through 12-32) as well as the SNRIs (serotonin norepinephrine

FIGURE 14-24A and B Benzodiazepine agonist spectrum in panic disorder. A theory about the biological basis of anxiety disorders, and particularly panic disorder, is that there is an abnormality in the set point for benzodiazepine receptors. Perhaps the normal sensitivity of these receptors (A) is switched to the left in this spectrum (B), rendering the receptors less sensitive to full agonists and experiencing antagonists as inverse agonists.
Potential Therapeutic Effects of GABA-ergic Agents

**FIGURE 14-25 Potential therapeutic effects of GABA-ergic agents.** (A) Pathological anxiety/fear may be caused by overactivation of amygdala circuits. (B) GABA-ergic agents such as benzodiazepines may alleviate anxiety/fear by enhancing phasic inhibitory actions at postsynaptic GABA-A receptors within the amygdala.

reuptake inhibitors; also discussed in Chapter 12; their mechanism of action is illustrated in Figures 12-33 through 12-42).

A serotonin 1A partial agonist, buspirone, is recognized as a generalized anxiolytic but not as a treatment for anxiety disorder subtypes. A related compound, gepirone ER, is in testing for major depression. Serotonin 1A partial agonists as augmenting agents to antidepressants are discussed in Chapter 12 and illustrated in Figure 12-129. Serotonin 1A partial agonist actions, also called SPA actions, which are among the mechanisms of atypical antipsychotic action, are discussed in Chapter 10 and illustrated in Figures 10-55 and 10-56.
FIGURE 14-26 Putative GABA mechanisms for novel anxiolytics. There are several potential ways to modulate GABA neurotransmission that could prove to be anxiolytic. Partial agonists that are selective for the alpha 2 or 3 subunits of the GABA-A receptor may, like current benzodiazepines that bind there, be anxiolytic yet may also cause less sedation and have less abuse potential than nonselective full agonist benzodiazepines. Inhibition of the GABA transporter (GAT) — for example, by the anticonvulsant tiagabine — has been shown to provide anxiolytic effects. Some anticonvulsants may increase GABA’s release or reduce its destruction via GABA transaminase (GABA-T), either of which could also have anxiolytic effects. Finally, it is possible that GABA-B receptors may play a role in anxiety; thus positive modulators of those receptors are potential therapeutic agents.

The potential anxiolytic actions of buspirone at both presynaptic and postsynaptic 5HT1A receptors are illustrated in Figure 14-28. Since the onset of anxiolytic action for buspirone is delayed, just as it is for antidepressants, this has led to the belief that 5HT1A agonists exert their therapeutic effects by virtue of adaptive neuronal events and receptor events rather than simply by the acute occupancy of 5HT1A receptors by the drug, as shown in Figure 14-28. In this way, the presumed mechanism of action of 5HT1A partial agonists is analogous to that of the antidepressants, which are also presumed to act by adaptations in neurotransmitter receptors, and different from that of the benzodiazepine anxiolytics, which act relatively acutely by occupancy of benzodiazepine receptors.

A simplified notion of how serotonergic anxiolytics might modulate excessive output from the amygdala, associated with anxiety and fear in various anxiety disorders, is shown in Figure 14-27. Excessive amygdala activity is theoretically reduced, after a delay, by enhancing the input of serotonin to key amygdala nuclei so as to blunt fear-associated outputs (see also Figures 14-10 through 14-15).

**Born fearful?**
Serotonin is involved not only in the therapeutic action of numerous proven anxiolytics for anxiety disorder subtypes (Figure 14-27) but also in regulating the efficiency of information processing in the amygdala and therefore the vulnerability or resilience of fear circuits.
Potential Therapeutic Effects of Serotonergic Agents

**FIGURE 14-27 A and B Potential therapeutic effects of serotonergic agents.** (A) Pathological anxiety/fear may be caused by overactivation of amygdala circuits. (B) 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.

(Figure 14-29). That is, the type of serotonin transporter (SERT) with which you are born determines whether your amygdala overreacts to fearful faces (Figure 14-29). It also determines how well you respond to stress and perhaps whether your brain atrophies with exposure to chronic stress or your anxiety disorder responds well to an SSRI/SNRI (Figure 14-29). Thus, can you be born fearful?

The processing of fearful faces is discussed in Chapter 8 and illustrated in Figures 8-11 through 8-20. Specifically, the excessive reaction of the amygdala to fearful faces for normal controls who are carriers of the “s” variant of the gene for SERT is shown in Figure 8-13 and is also represented as excessive amygdala activity in Figure 14-29. Under stress, this overactivity and inefficient information processing (Figures 8-13 and 14-29) may become an...
FIGURE 14-28 5HT1A partial agonist actions in anxiety. 5HT1A partial agonists such as buspirone may reduce anxiety by actions both at presynaptic somatodendritic autoreceptors (left) and at postsynaptic receptors (right). The onset of action of buspirone, like that of antidepressants, is delayed, suggesting that the therapeutic effects are actually related to downstream adaptive changes rather than acute actions at these receptors.

The overt symptom of anxiety (Figure 8-18) whether that symptom is part of a major depressive episode or a component of one of the anxiety disorder subtypes (Figure 8-17). Both GABA and serotonin regulate circuits in the amygdala (Figure 8-19), and benzodiazepines, SSRIs, SNRIs, and cognitive behavioral therapy can all potentially modify this circuitry to produce anxiolytic actions (Figure 8-20).

The point is that the specific gene that you have for the serotonin transporter can alter the efficiency of affective information processing by your amygdala and consequently your risk for developing an anxiety disorder or major depression if you experience multiple life stressors as an adult (Figure 14-29). Specifically, the “l” genotype of SERT is more resilient (Figure 14-29), with less reactivity to fearful faces (Figures 8-13 and 13-29), less likelihood of breaking down into a major depressive episode or anxiety disorder when exposed to multiple life stressors (Figure 14-29), and perhaps less vulnerability to atrophy of the hippocampus (Figure 14-29) and greater likelihood of responding to treatment with SSRIs if an anxiety disorder is present.

On the other hand, the “s” genotype is apparently more vulnerable, overreacting to fearful faces (Figures 8-13 and 14-29), more likely to develop an affective disorder when exposed to multiple life stressors, and possibly associated with more hippocampal atrophy and less responsiveness to SSRI treatment (Figure 14-29). Whether you have the "l" or the "s" genotype of SERT accounts for only a small amount of the variance for whether or not you will develop an anxiety disorder under stress and thus does not totally predict who will develop an anxiety disorder and who will not. However, this example does prove...