01 - 6 Mood Disorders and the Neurotransmitter Net

6 Mood Disorders and the Neurotransmitter Networks Norepinephrine and γ-Aminobutyric Acid (GABA)

Mood Disorders and the Neurotransmitter Networks Norepinephrine and γ-Aminobutyric Acid (GABA) Description of Mood Disorders 244 Mood Spectrum 244 Distinguishing Unipolar Depression from Bipolar Depression 249 Mixed Features: Are Mood Disorders Progressive? 251 Neurobiology of Mood Disorders 252 Neurotransmitters 252 The Monoamine Hypothesis of Depression 264 The Monoamine Receptor Hypothesis and Neurotrophic Factors 264 Beyond Monoamines: The Neuroplasticity and Neuroprogression Hypothesis of Depression 266 Symptoms and Circuits in Mood Disorders 277 Symptom-Based Treatment Selections 279 Summary 282 action and how to select specific drug treatments in Chapter 7. DESCRIPTION OF MOOD DISORDERS Mood Spectrum Disorders of mood are often called affective disorders, since affect is the external display of mood, an emotion that is, however, felt internally and called mood. Mood disorders are not just about mood. The diagnosis of a major depressive episode requires the presence of at least five symptoms, only one of which is depressed mood (Figure 6-1). Similarly, a manic episode requires more than just an elevated, expansive, or irritable mood; there must be at least three or four additional symptoms (Figure 6-2). Classically, the mood symptoms of mania and depression are “poles” apart (Figures 6-3 through 6-6). This concept has generated the terms “unipolar” depression (i.e., patients who experience just the down or depressed pole) (Figures 6-3 and 6-4) and “bipolar” (i.e., patients who at different times experience the up pole, or mania (Figures 6-3 and 6-5) or hypomania (Figures 6-3 and 6-6) and the down pole, i.e., depressed pole (Figures 6-3, 6-5, and 6-6). Bipolar I patients have full-blown manic episodes usually followed by depressive episodes (Figure 6-5). Bipolar II disorder is characterized by at least one hypomanic episode and one major depressive episode (Figure 6-6). Depression and mania may even occur simultaneously, which is This chapter discusses disorders characterized by abnormalities of mood: namely, depression, mania, or mixtures of both. Included here are descriptions of a wide variety of mood disorders that occur over a broad clinical spectrum. Clinical descriptions and criteria for how to diagnose disorders of mood will only be mentioned in passing. The reader should consult standard reference sources for this material. Also included in this chapter is an analysis of how monoamine neurotransmitter systems have long been hypothetically linked to the biological basis of mood disorders. We will also cover more recent advances in neurobiology that link mood disorders to glutamate, GABA (γ-aminobutyric acid), neurotrophic factors, neuroinflammation, and stress. Mood disorders have many symptoms and approaching them clinically involves first constructing a diagnosis from a given patient's symptom profile, but then deconstructing that patient's mood disorder into its component symptoms so each symptom can be individually targeted therapeutically. We will discuss how to combine this clinical approach to diagnosis with a neurobiological approach to treatment by first matching every symptom to its hypothetically malfunctioning brain circuit, regulated by one or more neurotransmitters. The strategy is next to select drugs that target the specific neurotransmitters in the specific symptomatic brain circuits in a given patient. The goal is to improve the efficiency of information processing in those brain circuits and thereby reduce symptoms. Covering the neurobiological basis of mood disorders in this chapter sets the stage for understanding the mechanisms of

Chapter 6: Mood Disorders apathy/ loss of interest sleep disturbances psychomotor fatigue suicidal ideation guilt worthlessness executive dysfunction or depressed mood Symptom Dimensions of a Major Depressive Episode one of these required four more of these required weight/ appetite changes Figure 6-1 DSM-5 symptoms of a major depressive episode. According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), a major depressive episode consists of either depressed mood or loss of interest and at least four of the following: weight/appetite changes, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of guilt or worthlessness, executive dysfunction, and suicidal ideation. Figure 6-2 DSM-5 symptoms of a manic episode. According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), a manic episode consists of either elevated/expansive mood or irritable mood. In addition, at least three of the following must be present (four if mood is irritable): inflated self-esteem/grandiosity, increased goal-directed activity or agitation, risk taking, decreased need for sleep, distractibility, pressured speech, and racing thoughts. increased goal-directed activity or agitation risk taking decreased need for sleep more talkative pressured speech flight of ideas/ racing thoughts inflated selfesteem/ grandiosity distractible/ concentration Symptom Dimensions of a Manic Episode symptoms necessary for diagnosis plus three or more of these (four if mood is only irritable) elevated/expansive mood irritable mood and then I went there and then the next place and so on and then over to there and then the market and then a dog was barking and then I saw a kitty and then the dog started chasing the kitty and then I went into the market and I bought some cheese and some salad and dressing and

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY HYPOMANIA MIXED FEATURES OF MANIA MIXED FEATURES OF DEPRESSION depression mania hypomania mixed features of depression mixed features of mania Figure 6-3 Mood episodes. Mood symptoms exist along a spectrum, with the polar ends being pure mania or hypomania (”up” pole) and pure depression (”down” pole). Patients can also experience mood episodes that include symptoms of both poles; such episodes can be described as mania/hypomania with mixed features of depression or depression with mixed features of mania. A patient may have any combination of these episodes over the course of illness; subsyndromal manic or depressive episodes also occur during the course of illness, in which case there are not enough symptoms or the symptoms are not severe enough to meet the diagnostic criteria for one of these episodes. Thus the presentation of mood disorders can vary widely. HYPOMANIA MIXED FEATURES OF MANIA MIXED FEATURES OF DEPRESSION Major Depressive Disorder Single Episode or Recurrent Unipolar single episode recurrent Figure 6-4 Major depressive disorder. Major depressive disorder is defined by the occurrence of at least a single major depressive episode, although most patients will experience recurrent episodes.

6 HYPOMANIA MIXED FEATURES OF MANIA MIXED FEATURES OF DEPRESSION Bipolar I Disorder Manic Episode +/– Major Depressive Episode manic manic with mixed features depressive (after manic episode) Figure 6-5 Bipolar I disorder. Bipolar I disorder is defined as the occurrence of at least one manic episode. Patients with bipolar I disorder typically experience major depressive episodes as well, although this is not necessary for the bipolar I diagnosis. It is also common for patients to experience manic episodes with mixed features of depression. HYPOMANIA Bipolar II Disorder Major Depressive and Hypomanic Episodes Figure 6-6 Bipolar II disorder. Bipolar II disorder is defined as an illness course consisting of one or more major depressive episodes and at least one hypomanic episode.

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY called a “mixed” mood state or, in DSM-5, “mixed features” (Figure 6-7; Table 6-1). Introduction of the mixed-features modifier has moved the field away from considering depression and mania as distinct categories Mood Disorder Spectrums depression with mixed features mania with mixed features Figure 6-7 Mood-disorder spectrums. Depressive symptoms and manic symptoms can occur as part of the same episode; this is termed “mixed features” and can be defined as depression with mixed features, in which depressive symptoms dominate, or as mania with mixed features, in which manic symptoms dominate. Thus mood disorders are best understood as a spectrum, rather than as discrete categorial diagnoses. Table 6-1 Mixed features (DSM-5) of manic, hypomanic, and major depressive episodes Manic or hypomanic episode, with mixed features Full criteria for manic or hypomanic episode At least three of the following symptoms of depression: Depressed mood Loss of interest or pleasure Psychomotor retardation Fatigue or loss of energy Feelings of worthlessness or excessive or inappropriate guilt Recurrent thoughts of death or suicidal ideation/actions Depressive episode, with mixed features Full criteria for a major depressive episode At least three of the following manic/hypomanic symptoms: Elevated, expansive mood (e.g., feeling high, excited, or hyper) Inflated self-esteem or grandiosity More talkative than usual or feeling pressured to keep talking Flight of ideas or subjective experience that thoughts are racing Increase in energy or goal-directed activity Increased or excessive involvement in activities that have a high potential for painful consequences Decreased need for sleep (*Not included: psychomotor agitation) (*Not included: irritability) (*Not included: distractibility) and towards the concept that they are opposite ends of a spectrum, with all degrees of mixtures in between (Figure 6-7). Many real patients are neither purely depressed nor purely manic, but some mixture of both,

Chapter 6: Mood Disorders Distinguishing Unipolar Depression from Bipolar Depression Other than a history of a prior manic/hypomanic episode, patients with unipolar depressive episodes (Figure 6-4) are diagnosed using the same symptom criteria (Figure 6-1) as patients with bipolar depressive episodes (Figures 6-5 and 6-6). Despite similar symptoms, patients with with the specific mix of symptoms changing along the mood spectrum over the course of illness. This is similar to the evolution in the conceptualization of schizophrenia versus bipolar disorder, where the old dichotomous model (Figure 6-8) has been largely replaced with a continuous disease model spectrum, ranging from pure psychotic disorder to pure mood disorder (Figure 6-9). Dichotomous Disease Model Schizophrenia Schizophrenia and Bipolar Disorder • psychosis • chronic, unremitting • poor outcome • “even a trace of schizophrenia is schizophrenia” Schizoaffective Disorder • psychosis • mood disorder Bipolar Disorder • mania • mood disorder • cyclical • good outcome • “even a trace of a mood disturbance is a mood disorder” Figure 6-8 Schizophrenia and bipolar disorder: dichotomous disease model. Schizophrenia and bipolar disorder have been conceptualized both as dichotomous disorders and as belonging to a continuum. In the dichotomous disease model, schizophrenia consists of chronic, unremitting psychosis, with poor outcomes expected. Bipolar disorder consists of cyclical manic and other mood episodes and has better expected outcomes than schizophrenia. A third distinct disorder is schizoaffective disorder, characterized by both psychosis and a mood disorder. brief psychotic disorder delusional disorder shared psychotic disorder subsyndromal paranoid schizotypal schizoid avoidant ultra high risk psychosis prodrome schizophrenia schizophreniform disorder schizoaffective disorder mood disorder depression atypical depression seasonal affective disorder melancholia catatonic depression mixed mania/depression postpartum depression psychotic depression Continuum Disease Model Schizophrenia and Bipolar Disorder Figure 6-9 Schizophrenia and bipolar disorder: continuum disease model. Schizophrenia and bipolar disorder have been conceptualized both as dichotomous disorders and as belonging to a continuum. In the continuum disease model, schizophrenia and mood disorders fall along a continuum in which psychosis, delusions, and paranoid avoidant behavior are on one extreme and depression and other mood symptoms are on the other extreme. Falling in the middle are psychotic depression and schizoaffective disorder.

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY may lead to worse quality of life due to giving the wrong treatment (for unipolar depression rather than for bipolar depression) and this may be ineffective or even dangerous. That is, delay of appropriate treatment in bipolar depression can increase the risk of mood cycling, relapse, and suicide, and even decrease the chances of responding to appropriate bipolar treatments once they are given later. Thus, it is important to tell unipolar from bipolar depression. Is there any way to do this when the patient is in the depressed state other than to find a prior history of mania/hypomania? The short answer is no. The long answer is that there are certain clinical characteristics that favor the likelihood of a bipolar depressive episode instead of a unipolar depressive episode, and these factors can be clues to the diagnosis of a bipolar depressive episode when the past history of a manic/hypomanic episode is unclear (Figure 6-10). Some additional tips about how to determine whether a depressed patient is unipolar or bipolar might be to ask two questions (Table 6-2): “Who’s your daddy?” and “Where’s your mama?” unipolar versus bipolar depression have different longterm outcomes and should generally receive different treatments. Unfortunately, missed diagnosis or delayed diagnosis of bipolar depression is all too common. Over a third of patients with unipolar depression are eventually re-diagnosed as having bipolar disorder and maybe as many as 60% of depressed patients with bipolar II disorder are initially diagnosed as having unipolar depression. In some cases, this is because the patient had depressive episodes before they had manic or hypomanic episodes, and a bipolar diagnosis could not be made. In other cases, the diagnosis of a past manic or hypomanic episode is missed because patients with bipolar disorder often present in the depressed phase and past hypomania is often pleasant for patients and may not be mentioned.

Why do you want to make an early accurate diagnosis of bipolar disorder? Although unipolar versus bipolar depression cannot be readily distinguished on the basis of a patient’s current symptomatology, there are some hints that can raise suspicion of a bipolar depressive episode rather than a unipolar depressive episode (Figure 6-10). Missing the diagnosis of bipolar depression early HYPOMANIA More: Family history of bipolar disorder Family history of substance abuse Comorbid substance abuse Suicide attempts Early age of onset <25 years Irritability Psychotic symptoms Mood reactivity Restlessness Psychomotor agitation (BPII) Psychomotor retardation (BPI) Shorter depressive episodes More previous depressive episodes Guilt Melancholia BIPOLAR DEPRESSION Identifying Bipolar Depression Figure 6-10 Identifying bipolar depression. Although all symptoms of a major depressive episode can occur in either unipolar or bipolar depression, some factors can provide hints if not diagnostic certainty that the patient has a bipolar spectrum disorder. These can include a family history of bipolar disorder, family history of substance abuse, comorbid substance abuse, history of suicide attempts, earlier age of onset, and shorter but more frequent depressive episodes. Some symptoms may also be more common as part of a bipolar illness, including irritability, psychotic symptoms, mood reactivity, restlessness, psychomotor agitation or retardation, guilt, and melancholia.

Table 6-2 Is it unipolar or bipolar depression? Questions to ask Who’s your daddy? What is your family history of: • mood disorder? • psychiatric hospitalizations? • suicide? • anyone who took lithium, mood stabilizers, drugs for psychosis or depression? • anyone who received ECT? These can be indications of a unipolar or bipolar spectrum disorder in relatives. Where’s your mama? I need to get additional history about you from someone close to you, such as your mother or your spouse. Patients may especially lack insight about their manic symptoms and under-report them. “Who’s your daddy?” means more precisely, “what is your family history?” since a first-degree relative with a bipolar spectrum disorder can give a strong hint that the patient also has a bipolar spectrum disorder rather than unipolar depression. Although the majority of patients with bipolar depression do not have a family history of bipolar disorder, when it is present, it is arguably the most robust and reliable risk factor for bipolar depression. Individuals with a first-degree relative with bipolar disorder are at an 8–10-fold greater risk of developing bipolar disorder compared to the general population. The second question, “Where’s your mama?,” really means “I need to get additional history from someone else close to you,” since patients tend to under-report their manic symptoms. The insight and observations of an outside informant such as a mother or spouse who can give past history might indeed prove to be quite different from the one the patient is reporting, and thus help establish a bipolar spectrum diagnosis that patients themselves deny or do not perceive. Mixed Features: Are Mood Disorders Progressive? In addition to the importance of distinguishing unipolar depression from bipolar depression, it is also very important to look for mixed features in your depressed patients, whether those patients have a unipolar or bipolar illness. This is because there are big differences in the outcome for patients if mixed features are present. Chapter 6: Mood Disorders For one thing, there is evidence that unipolar depression can progress to mixed features, mixed features progress to bipolar disorder, and bipolar disorder progress to treatment resistance (Figure 6-11). The presence of even subthreshold manic symptoms is strongly associated with conversion to bipolar disorder, with each manic symptom increasing risk by 30%. We don’t know if we can halt this march towards a bad outcome, but the best chance may be early recognition and effective treatment that reduces or eliminates all symptoms, whether manic or depressed, and to do this as early in the course of illness as possible. How many depressed patients have mixed features? The estimates are about a quarter of all patients with unipolar depression and a third of all patients with bipolar I or II depression have subsyndromal symptoms of mania. Estimates of mixed features in unipolar depression in children and adolescents are even higher. Compared to those with “pure” depression, those with depression plus some manic symptoms may have a more complex illness and less favorable course and outcome. For example, mixed features may compound the already high risk of suicide in depressed patients. Non-euphoric manic symptoms such as psychomotor agitation, impulsivity, irritability, and racing/crowded thoughts combined with depressive symptoms are a recipe for suicidality. Suicide rates are twice as high in bipolar than in unipolar depression and up to 20 times higher in bipolar disorder compared to the general population. Sadly, up to a third of bipolar patients attempt suicide at least once in their life, and 10–20% of them succeed. What about those subsyndromal manic symptoms and suicide? In the presence of mixed features there is a fourfold increased risk of suicidality in both unipolar and bipolar depression. Studies show specifically a worrisome association of mixed episodes with suicide attempts, so it is not only important to identify who has mixed features, but also to treat appropriately. Treatment for mixed features is discussed in Chapter 7 and surprisingly is NOT the same as the treatment for unipolar depression without mixed features. That is, neither unipolar nor bipolar depression with mixed features are treated first-line with standard monoamine reuptake inhibiting drugs used widely in unipolar depression and discussed in Chapter 7, but rather with serotonin/dopamine antagonists/partial agonists used widely for the treatment of psychosis and discussed in Chapter 5. Thus, it cannot be emphasized too strongly that major depressive episodes need to be correctly diagnosed as part of a unipolar or bipolar illness and as having or lacking mixed features, and that 251

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY mood disorders are hypothesized to involve dysfunction of various combinations of these neurotransmitters and ion channels, and all known treatments for mood disorders act upon one or more of them. We have extensively discussed the dopamine system (Chapter 4; Figures 4-2 through 4-13), the serotonin system (Chapter 4; Figures 4-36 through 4-51), the glutamate system (Chapter 4; Figures 4-20 through 4-28), and ion channels (Chapter 3; Figures 3-19 through 3-26). Here, we add two other neurotransmitter systems: norepinephrine and GABA. Before discussing how these various neurotransmitters and ion channels are thought to be involved in mood disorders, we will begin with a general discussion of norepinephrine, GABA, and their receptors and pathways. Norepinephrine The noradrenergic neuron utilizes norepinephrine (noradrenaline) as its neurotransmitter. Norepinephrine is synthesized, or produced, from the precursor amino acid tyrosine, which is transported into the nervous system from the blood by means of the correct treatment be given (details of treatment of mood disorders are given in Chapter 7). The hope is that recognition and appropriate treatment of both unipolar and bipolar depression – whether that depressive episode has mixed features or not – will cause all symptoms to remit for long periods of time and that this might prevent progression to more difficult states (Figure 6-11). This is not proven, but is a major hypothesis in the field at the present time. NEUROBIOLOGY OF MOOD DISORDERS Neurotransmitters Dysfunctional neurotransmission in various brain circuits is implicated in both the pathophysiology and treatment of mood disorders. Classically, this has included the monoamine neurotransmitters norepinephrine, dopamine, and serotonin, and more recently the neurotransmitters glutamate and GABA (γ-aminobutyric acid) and their associated ion channels. Symptoms of HYPOMANIA MIXED FEATURES OF MANIA MIXED FEATURES OF DEPRESSION recurrent unipolar depression mixed features mania or hypomania treatment resistance Is Major Depressive Disorder Progressive? Figure 6-11 Is major depressive disorder progressive? There is evidence that mood disorders may be progressive.

Unipolar depression with recurrent episodes may progress to depression with mixed features, which may ultimately progress to a bipolar spectrum condition and finally treatment resistance.

Chapter 6: Mood Disorders synthetic enzyme, dopamine β-hydroxylase (DBH), converts DA into NE. Norepinephrine is then stored in synaptic packages called vesicles until released by a nerve impulse (Figure 6-12). Norepinephrine action is terminated by two principal destructive or catabolic enzymes that turn NE into inactive metabolites. The first is monoamine oxidase (MAO) A or B, which is located in mitochondria in the presynaptic neuron and elsewhere (Figure 6-13). The second is catechol-O-methyltransferase (COMT), which is thought to be located largely outside of the presynaptic nerve terminal (Figure 6-13). The action of NE can be an active transport pump (Figure 6-12). Once inside the neuron, tyrosine is acted upon by three enzymes in sequence: first, tyrosine hydroxylase (TOH), the rate-limiting and most important enzyme in the regulation of norepinephrine (NE) synthesis. Tyrosine hydroxylase converts the amino acid tyrosine into DOPA. The second enzyme then acts, namely, DOPA decarboxylase (DDC), which converts DOPA into dopamine (DA). Dopamine itself is a neurotransmitter in DA neurons as discussed in Chapter 4 and illustrated in Figure 4-2. However, for NE neurons, DA is just a precursor of NE. In fact, the third and final NE NE (norepinephrine) TOH TYR DOPA

tyrosine transporter Norepinephrine Is Produced E E E DDC VMAT2 DBH Figure 6-12 Norepinephrine is produced. Tyrosine (TYR), a precursor to norepinephrine (NE), is taken up into NE nerve terminals via a tyrosine transporter and converted into DOPA by the enzyme tyrosine hydroxylase (TOH). DOPA is then converted into dopamine (DA) by the enzyme DOPA decarboxylase (DDC). Finally, DA is converted into NE by dopamine β-hydroxylase (DBH). After synthesis, NE is packaged into synaptic vesicles via the vesicular monoamine transporter 2 (VMAT2) and stored there until its release into the synapse during neurotransmission.

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY is the vesicular monoamine transporter 2 (VMAT2), which transports NE in the cytoplasm of the presynaptic neuron into storage vesicles (Figure 6-14). The VMAT2 transporter was extensively discussed in Chapter 5, as the VMAT2 transporter in dopamine nerve terminals is the target of treatments for tardive dyskinesia (Figures 5-10 through 5-12). Other NE receptors are classified as α1, α2A, α2B, or α2C, or as β1, β2, or β3 (Figure 6-14). All can be postsynaptic, but only α2 receptors can act as presynaptic autoreceptors (Figures 6-14 through 6-16). Postsynaptic receptors convert their occupancy by NE into physiological functions, and ultimately, into changes in signal transduction and gene expression in the postsynaptic neuron (Figure 6-14). Presynaptic α2 receptors regulate NE release, so they are called “autoreceptors” (Figures 6-14 and 6-15). Presynaptic α2 autoreceptors are located both on the axon terminal (i.e., terminal α2 receptors; Figures 6-14 and 6-15) and at the cell body (soma) and nearby dendrites; terminated not only by enzymes which destroy NE, but also by a transport pump for NE that removes it from acting in the synapse without destroying it (Figure 6-14). In fact, such inactivated NE can be restored for reuse in a later neurotransmitting nerve impulse. The transport pump that terminates synaptic action of NE is sometimes called the “NE transporter” or “NET” and sometimes the “NE reuptake pump.” This NE reuptake pump is located on the presynaptic noradrenergic nerve terminal as part of the presynaptic machinery of the neuron, where it acts as a vacuum cleaner whisking NE out of the synapse, off the synaptic receptors, and stopping its synaptic actions. Once inside the presynaptic nerve terminal, NE can either be stored again for subsequent reuse when another nerve impulse arrives, or it can be destroyed by NE-destroying enzymes (Figure 6-13). The noradrenergic neuron is regulated by a multiplicity of receptors for NE (Figure 6-14). The norepinephrine transporter is one type of receptor, as NE Norepinephrine Action Is Terminated norepinephrine transporter (NET) E E MAO A or B destroys NE COMT destroys NE Figure 6-13 Norepinephrine's action is terminated. Norepinephrine's action can be terminated through multiple mechanisms. Norepinephrine can be transported out of the synaptic cleft and back into the presynaptic neuron via the norepinephrine transporter (NET), where it may be repackaged for future use. Alternatively, norepinephrine may be broken down extracellularly via the enzyme catechol-O-methyltransferase (COMT). Other enzymes that break down norepinephrine are monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B), which are present in mitochondria, both within the presynaptic neuron and in other cells, including neurons and glia.

Chapter 6: Mood Disorders stimulating the presynaptic α2 neuron, but other drugs that antagonize this same receptor will have the effect of cutting the brake cable, thus enhancing release of NE. GABA (γ-Aminobutyric Acid) GABA is the principle inhibitory neurotransmitter in the brain, and normally serves an important regulatory role in reducing the activity of many neurons. Specifically, GABA is produced, or synthesized, from the amino acid glutamate (glutamic acid) via the actions of the enzyme glutamic acid decarboxylase (GAD) (Figure 6-17). Once formed in presynaptic neurons, GABA is transported into synaptic vesicles by vesicular inhibitory amino acid transporters (VIAATs), where it is stored until released into the synapse during inhibitory neurotransmission thus, these latter α2 presynaptic receptors are called somatodendritic α2 receptors (Figure 6-16). Presynaptic α2 receptors are important because both the terminal and the somatodendritic α2 receptors are autoreceptors. That is, when presynaptic α2 receptors recognize NE, they turn off further release of NE (Figures 6-14 and 6-15). Thus, presynaptic α2 autoreceptors act as a brake for the NE neuron, and also cause what is known as a negative feedback regulatory signal. Stimulating this receptor (i.e., stepping on the brake) stops the neuron from firing. This probably occurs physiologically to prevent over-firing of the NE neuron, since it can shut itself off once the firing rate gets too high and the autoreceptor becomes stimulated. It is worthy to note that some drugs can not only mimic the natural functioning of the NE neuron by Norepinephrine Receptors presynaptic alpha-2 autoreceptor norepinephrine transporter (NET) VMAT2 beta-1 receptor beta-2 receptor beta-3 receptor alpha-1 receptor postsynaptic alpha-2A receptor postsynaptic alpha-2C receptor postsynaptic alpha-2B receptor Figure 6-14 Norepinephrine receptors. Shown here are receptors for norepinephrine that regulate its neurotransmission. The norepinephrine transporter (NET) exists presynaptically and is responsible for clearing excess norepinephrine out of the synapse. The vesicular monoamine transporter 2 (VMAT2) takes norepinephrine up into synaptic vesicles and stores it for future neurotransmission. There is also a presynaptic α2 autoreceptor, which regulates release of norepinephrine from the presynaptic neuron. In addition, there are several postsynaptic receptors. These include α1, α2A, α2B, α2C, β1, β2, and β3 receptors.

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY alpha-2 adrenergic presynaptic autoreceptor NE occupying alpha-2 adrenergic presynaptic autoreceptor halts release of NE A B NE Figure 6-15 Alpha-2 receptors on axon terminal. Shown here are presynaptic α2-adrenergic autoreceptors located on the axon terminal of the norepinephrine (NE) neuron. These autoreceptors are "gatekeepers" for norepinephrine. (A) When they are not bound by norepinephrine, they are open, allowing norepinephrine release. (B) When norepinephrine binds to the gatekeeping receptors, they close the molecular gate and prevent norepinephrine from being released.

Chapter 6: Mood Disorders A B somatodendritic alpha-2 adrenergic autoreceptor NE occupying somatodendritic alpha-2 adrenergic autoreceptor causes a decrease in firing and a decrease of NE release Figure 6-16 Somatodendritic α2 receptors. Shown here are presynaptic α2-adrenergic autoreceptors located in the somatodendritic area of the norepinephrine neuron. (A) When they are not bound by norepinephrine, there is normal neuronal impulse flow, with resultant release of norepinephrine. (B) When norepinephrine binds to these α2 receptors, it shuts off neuronal impulse flow (see loss of lightning bolts in the neuron), and this stops further norepinephrine release.

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY (Figure 6-17). GABA's synaptic actions are terminated by the presynaptic GABA transporter (GAT), also known as the GABA reuptake pump (Figure 6-18), analogous to similar transporters for other neurotransmitters discussed throughout this text. GABA action can also be terminated by the enzyme GABA transaminase (GABA-T), which converts GABA into an inactive substance (Figure 6-18). There are three major types of GABA receptors and numerous subtypes of GABA receptors. The major types are GABAA, GABAB, and GABAC receptors (Figure 6-19). GABAA and GABAC receptors are both ligand-gated ion channels, whereas GABAB receptors are linked to G proteins and not to ion channels (Figure 6–19). GABAA Receptor Subtypes The molecular structure of GABAA receptors is shown in Figure 6-20. Each subunit of a GABAA receptor has four transmembrane regions (Figure 6-20A). When five subunits cluster together, they form an intact GABAA receptor with a chloride channel in the center (Figure 6-20B). There are many different subtypes of GABA Action Is Terminated GABA-T destroys GABA E GABA transporter (GAT) GABA GABA Is Produced glutamate GABA E GAD VIAAT GABA Figure 6-17 Gamma-aminobutyric acid (GABA) is produced. The amino acid glutamate, a precursor to GABA, is converted to GABA by the enzyme glutamic acid decarboxylase (GAD). After synthesis, GABA is transported into synaptic vesicles via vesicular inhibitory amino acid transporters (VIAATs) and stored until its release into the synapse during neurotransmission. Figure 6-18 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).

GABA transporter (GAT) A GABA receptor B GABA receptor complex GABA receptor complex GABAA receptors, depending upon which subunits are present (Figure 6-20C). Subunits of GABAA receptors are sometimes also called isoforms, and include α (with six isoforms α1 to α6), β (with three isoforms β1 to β3), γ (with three isoforms γ1 to γ3), δ, ε, π, θ, and ρ (with three isoforms ρ1 to ρ3) (Figure 6-20C). What is important for this discussion is that depending upon which subunits are present, the functions of a GABAA receptor can vary quite significantly. Thus, GABAA receptors can be classified by the specific isoform subunits that they contain. GABAA receptors can also be categorized into other subtypes: those that are synaptic and hypothetically mediate phasic neurotransmission, and those that are extrasynaptic and hypothetically mediate tonic neurotransmission (Figure 6-21). Other classification systems are whether GABA receptors are sensitive to the well-known benzodiazepines or insensitive to them. Some of these classifications overlap, since GABAA Chapter 6: Mood Disorders GABA Receptors Figure 6-19 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: GABAA, GABAB, and GABAC. GABAA and GABAC receptors are ligand-gated ion channels; they are part of a macromolecular complex that forms an inhibitory chloride channel. GABAB receptors are G-protein-linked receptors that may be coupled with calcium or potassium channels. GABA C receptors containing a γ subunit tend to be synaptic, to mediate phasic neurotransmission, and to be sensitive to benzodiazepines. On the other hand, GABAA receptors containing a δ subunit tend to be extrasynaptic, to mediate tonic neurotransmission, and to be insensitive to benzodiazepines. Benzodiazepine-sensitive GABAA receptors have several structural and functional features that make them distinct from benzodiazepine-insensitive GABAA receptors. For a GABAA receptor to be sensitive to benzodiazepines, there must be two β units plus a γ unit of either the γ2 or γ3 subtype, plus two α units of either the α1, α2, or α3 subtype (Figure 6-20C). Benzodiazepines appear to bind to the region of the receptor between the γ2/γ3 subunit and the α1/α2/α3 subunit, one benzodiazepine molecule per receptor complex (Figure 6-20C). GABA itself binds with two molecules of GABA per receptor complex, to the GABA agonist sites in the 259

Structure of GABA Receptors five substructures form the receptor complex inhibition the chloride channel is at the center cytoplasmic loop transmembrane region extracellular amino acid chains four transmembrane regions make up one subunit Major Subtypes of GABA Receptors C B A (1-6) (1-3)

1-3 or ( )) -anxiolytic -phasic inhibition -synaptic 2, 1 2, 1 2 3 6 GABA binding site BZ binding site GABA binding site BZ binding site BZ binding site GABA binding site neuroactive steroids -alcohol -general anesthetics -tonic inhibition -extrasynaptic ß 2, ( ) 4, (ß ß -sedative -phasic inhibition A A GABA binding site Figure 6-20 Gamma-aminobutyric acid A (GABAA) receptors. (A) Shown here are the four transmembrane regions that make up one subunit of a GABAA receptor. (B) There are five copies of these subunits in a fully constituted GABAA 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 GABAA receptor. These include six different α isoforms, three different β isoforms, three different γ isoforms, δ, ε, π, θ, and three different ρ isoforms. The ultimate type and function of each GABAA receptor subtype will depend on which subunits it contains. Benzodiazepine (BZ)-sensitive GABAA receptors (middle two) contain two β units, plus either γ2 or γ3, plus two α (α1 through α3) subunits. They generally mediate phasic inhibition triggered by peak concentrations of synaptically released GABA. Benzodiazepine-sensitive GABAA receptors containing α1 subunits are involved in sleep (second from left), while those that contain α2 and/or α3 subunits are involved in anxiety (second from right). GABAA receptors containing α4, α6, or δ subunits (far right) are benzodiazepine-insensitive, are located extrasynaptically, and regulate tonic inhibition. They are bound by naturally occurring neuroactive steroids and possibly to alcohol and some general anesthetics.

regions of the receptor between the α and the β units, sometimes also referred to as the GABA orthosteric site (Figures 6-20C and 6-22). Acting alone, GABA acting at its agonist sites can increase the frequency of opening of the chloride channel formed inside all its subunits (see Figure 6-20), but only to a limited extent (compare Figure 6-22A and 6-22B). Since the site for benzodiazepines is in a different location from the agonist sites for GABA (see Figure 6-20C and 6-22D), the modulatory site is often called allosteric (literally “other site”), and the agents that bind there “allosteric modulators.” Since the modulation is “positive” in the sense that it makes GABA more effective at GABAA receptors, enhancing the frequency of opening of inhibitory chloride channels (Figure 6-22D), the action is called “positive allosteric modulation,” and benzodiazepines are called GABAA positive allosteric modulators (PAMs). Interestingly, GABA must be present for the PAM to work (compare Figure 6-22C and 6-22D). The actions of benzodiazepines at benzodiazepinesensitive GABAA receptors are essentially the actions Two Types of GABAA Mediated Inhibition GABA neuron GABA GABAA GABA 1, 3) (A 4, 6) (postsynaptic extrasynaptic tonic inhibition phasic inhibition Chapter 6: Mood Disorders of an agonist at their positive allosteric sites, because their actions can be reversed by the neutral antagonist flumazenil (Figure 6-23), which is sometimes used to reverse anesthesia with benzodiazepines or overdoses of benzodiazepines. As mentioned above, benzodiazepine-sensitive GABAA receptor subtypes (with γ subunits and α1 to α3 subunits) are thought to be postsynaptic and to mediate a type of inhibition at the postsynaptic neuron that is phasic, occurring in bursts of inhibition that are triggered by peak concentrations of synaptically released GABA (Figure 6-21). Theoretically, benzodiazepines acting at these receptors, particularly the α2/3 subtypes clustered at postsynaptic GABA sites, should exert an anxiolytic effect due to enhancement of phasic postsynaptic inhibition. However, not all benzodiazepine-sensitive GABAA receptors are the same. Notably, on the one hand, those benzodiazepine-sensitive GABAA receptors with α1 subunits may be most important for regulating sleep and are the presumed targets of numerous sedative hypnotic agents, including both benzodiazepine and Figure 6-21 GABAA mediation of tonic and phasic inhibition. Benzodiazepine-sensitive GABAA receptors (those that contain γ and α1 through α3 subunits) are postsynaptic receptors that mediate phasic inhibition, which occurs in bursts triggered by peak concentrations of synaptically released GABA. Benzodiazepine-insensitive GABAA receptors (those containing δ subunits and α4 or α6 subunits) are extrasynaptic and capture GABA that diffuses away from the synapse as well as neuroactive steroids 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). glial cell cholesterol mitochondria pregnenolone neuroactive steroid

chloride channel GABA binding site BZ binding site A A B C D = GABA = benzodiazepine non-benzodiazepine PAMs of the GABAA receptor (Figure 6-21C). The α1 subtype of GABAA receptors and the drugs that bind to it are discussed further in Chapter 10 on disorders of sleep. Some of these agents (i.e., some Z drugs that also bind to benzodiazepine-sensitive GABAA receptors; see Chapter 10) are selective for only the α1 subtype of GABAA receptor. On the other hand, benzodiazepine-sensitive GABAA receptors with α2 and/ or α3 subunits may be most important for regulating anxiety and are the presumed targets of the anxiolytic and Figure 6-22 Positive allosteric modulation of GABA-A receptors. (A) Benzodiazepine (BZ)-sensitive GABAA 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 GABAA 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 GABAA 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 GABAA receptor in the presence of GABA, it causes the channel to open even more frequently than when GABA alone is present. sedative hypnotic benzodiazepines (discussed in Chapter 8 on anxiety and in Chapter 10) (Figure 6-20C). Currently available benzodiazepines are nonselective for GABAA receptors with different α subunits. Abnormal expression of γ2, α2, or δ subunits have all been 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 psychiatric disorders, including different subpopulations of depression.

flumazenil = GABA = benzodiazepine = flumazenil Benzodiazepine-insensitive GABAA receptors are those with α4, α6, γ1, or δ subunits (Figure 6-20C). GABAA receptors with a δ subunit rather than a γ subunit, plus either α4 or α6 subunits, do not bind to benzodiazepines. Benzodiazepine-insensitive GABAA receptors bind instead to the naturally occurring neuroactive steroids, and possibly to alcohol and to some general anesthetics (Figure 6-20C). The binding site for these non-benzodiazepine modulators is located between the α and the δ subunits, one site per receptor complex (Figure 6-20C). Two molecules of GABA bind per receptor complex of benzodiazepine-insensitive GABAA receptors at the GABA agonist (orthosteric) sites located between the α and the β subunits (Figure 6-20C), just as they do at the benzodiazepine-sensitive GABAA receptors. As already mentioned, benzodiazepine-insensitive GABAA receptor subtypes (with δ subunits and α4 or α6 subunits) are thought to be located extrasynaptically, where they capture not only GABA that diffuses away from the synapse, but also neuroactive steroids synthesized and released by glia (Figure 6-21). Extrasynaptic benzodiazepine-insensitive GABAA 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 Chapter 6: Mood Disorders Figure 6-23 Flumazenil. The benzodiazepine receptor antagonist flumazenil is able to reverse a full agonist benzodiazepine acting at its site on the GABAA 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. benzodiazepine-sensitive GABAA receptors (Figure 6-21). Tonic inhibition may be regulated by the ambient levels of extracellular GABA molecules that have escaped presynaptic reuptake and enzymatic destruction and persist between neurotransmissions and is boosted by allosteric modulation at these sites. Thus, 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 neuroactive steroids have antidepressant properties (see Chapter 7), this has led to the proposal that some depressed patients may have a lack of normal tonic inhibition, and thus too much excitability in some brain circuits. Hypothetically this could be calmed by neuroactive steroid administration, causing more efficiency of information processing in those brain circuits and reduction of the symptoms of depression. It is possible that neuroactive steroids could also have important anxiolytic actions. Why would more tonic and supposedly sustained opening of chloride channels be a good thing for depression? In the case of postpartum depression, it may be potentially explainable on the basis that pregnant women have high circulating and presumably brain levels of neuroactive steroids. When they deliver, there is a precipitous decline 263

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY in circulating neuroactive steroid levels, hypothetically triggering the sudden onset of a major depressive episode when tonic inhibition is lost. Restoring neuroactive steroid levels – and tonic inhibition – for 60 hours of intravenous infusion may be enough for the patient to respond by reversing their depression and then having some additional time to accommodate to the lower levels of neuroactive steroids postpartum. This is a reasonable but not yet proven theory. It may be a bit more difficult to understand why positive allosteric modulation by a neuroactive steroid would treat other forms of depression, and treat quickly. However neuroactive steroids exert their antidepressant effects, clearly extrasynaptic benzodiazepine-insensitive GABAA sites are the targets, because benzodiazepines acting at the synaptic benzodiazepine-sensitive GABAA sites do not have robust antidepressant action. It may be worth noting that neuroactive steroids actually work at both benzodiazepine-sensitive GABAA receptors as well as at benzodiazepine-insensitive GABAA receptors. However, their unique action is at the benzodiazepine-insensitive sites and it is this action that is the focus of much interest in how neuroactive steroids hypothetically mediate their antidepressant actions. The Monoamine Hypothesis of Depression The classic theory about the biological etiology of depression hypothesizes that depression is due to a deficiency of monoamine neurotransmission. Mania may be the opposite, due to an excess of monoamine neurotransmission. This original conceptualization was a rather simplistic “chemical imbalance” notion that is now considered relatively unsophisticated and based mainly on observations that certain drugs that depleted monoamines could induce depression, and that all effective drugs for depression in the past acted by boosting one or more of three monoamine neurotransmitters: norepinephrine, serotonin, or dopamine. Thus, the idea was born that the “normal” amount of monoamine neurotransmitters (Figure 6-24A) somehow became depleted by an unknown disease process, stress, or drugs (Figure 6-24B), leading to the symptoms of depression. Direct evidence for the monoamine hypothesis is still largely lacking. A good deal of effort was expended especially in the 1970s and 1980s to identify the theoretically predicted deficiencies of monoamine neurotransmitters in depression and excess in mania. This effort to date has unfortunately yielded mixed results, prompting a search for better explanations of the etiology of mood disorders in general and of the potential link between monoamines and mood disorders in particular. The Monoamine Receptor Hypothesis and Neurotrophic Factors Because of these and other difficulties with the monoamine hypothesis, the focus of hypotheses for the etiology of mood disorders shifted next from the monoamine neurotransmitters themselves to their receptors and then to the downstream molecular events that these receptors trigger, including the regulation of gene expression and the production of growth factors. Currently, there is also great interest in the influence of nature (genes) and nurture (environment and epigenetics) on brain circuits regulated by monoamines, especially what happens when epigenetic changes from stressful life experiences are combined with inheriting various risk genes that can make an individual vulnerable to those environmental stressors. The neurotransmitter receptor hypothesis of depression posits that an abnormality in the receptors for monoamine neurotransmitters leads to depression (Figure 6-24B). Thus, if depletion of monoamine neurotransmitters is the central theme of the monoamine hypothesis of depression (Figure 6-24B), the neurotransmitter receptor hypothesis of depression takes this theme one step further: namely, that the depletion of neurotransmitter causes compensatory upregulation of postsynaptic neurotransmitter receptors (Figure 6-24C). Direct evidence for this hypothesis is also generally lacking. However, postmortem studies do consistently show increased numbers of serotonin 2 receptors in the frontal cortex of patients who die by suicide. Also, some neuroimaging studies have identified abnormalities in serotonin receptors of depressed patients, but this approach has not yet been successful in identifying consistent and replicable molecular lesions in receptors for monoamines in depression. Thus, there is no clear and convincing evidence that monoamine deficiency accounts for depression: i.e., there is no “real” monoamine deficit. Likewise, there is no clear and convincing evidence that abnormalities in monoamine receptors account for depression even though all the classic drugs to treat depression raise monoamine levels. Although the monoamine hypothesis is obviously an overly simplified notion about mood disorders, it has been very valuable in focusing attention upon the three monoamine neurotransmitters norepinephrine, dopamine, and serotonin. This has led to a much better understanding of the physiological

Monoamine Receptor Hypothesis of Depression NE 5HT DA normal state - no depression A depression - caused by monoamine deficiency B receptors upregulate due to lack of monoamines C Figure 6-24 Monoamine receptor hypothesis of depression. (A) According to the classic monoamine hypothesis of depression, when there is a “normal” amount of monoamine neurotransmitter activity, there is no depression present. (B) The monoamine hypothesis of depression posits that if the “normal” amount of monoamine neurotransmitter activity becomes reduced, depleted, or dysfunctional for some reason, depression may ensue. (C) The monoamine receptor hypothesis of depression extends the classic monoamine hypothesis of depression, positing that deficient activity of monoamine neurotransmitters causes upregulation of postsynaptic monoamine neurotransmitter receptors, and that this leads to depression.

administration of drugs for depression include the downstream synthesis of growth factors such as BDNF (brain-derived neurotrophic factor) (Figure 6-27). One notable current hypothesis is that stress, inflammation, and other genetic and environmental factors (such as early life adversity, the microbiome, and chronic medical illnesses) lead to loss of growth factors (Figure 6-28) and this leads in turn to neuroprogression, starting with lack of synaptic maintenance and then loss of synapses and dendritic arborization, and then ultimately leading to loss of neurons themselves (Figure 6-29, left), at which point neuroprogression becomes irreversible. The effect of the loss of growth factors on maintaining synaptic integrity and connectivity is shown in the microscopic inserts in Figure 6-30 (see loss of dendritic spines indicating loss of synapses on the right). Ominously, copious degrees of synaptic and neuronal loss can be observed on structural magnetic resonance imaging brain scans (Figure 6-30). Abnormal functional neuroimaging studies of connectivity of brain circuits have also been reported in depression. The hypothetical neurobiology of neuroprogression in depression is multifactorial (Figure 6-31). In addition to possibly deficient production of growth factors (Figures 6-27 through 6-29; 6-31), there is also the longstanding theory of hypothalamic-pituitary-adrenal (HPA) axis dysregulation in depression, and it, too, functioning of these three neurotransmitters, and for a while led to more and more pharmacological treatment options for depression, with many therapeutic variants upon the theme of monoamine targeting. These many therapeutic approaches and drugs are discussed in detail in Chapter 7. Beyond Monoamines: The Neuroplasticity and Neuroprogression Hypothesis of Depression One of the hints that depression is not simply due to deficient monoamines and that drugs for depression simply restored those deficient monoamines is the observation that the classic drugs for depression increased monoamines almost immediately, yet the clinical improvement in depression is delayed for weeks (Figure 6-25). This led to a search for molecular events that correlated in time with the onset of clinical antidepressant effects. Some of the earliest findings showed that delayed downregulation of neurotransmitter receptors following immediate elevation of monoamines after administration of drugs for depression correlates in time with the onset of clinical antidepressant effects (Figures 6-25 and 6-26). Downregulation of neurotransmitter receptors also correlates in time with the onset of tolerance to some of the side effects of drugs used to treat depression. Other molecular events that correlate with the timing of onset of clinical antidepressant effects following clinical effect Medication introduced amount of NT receptor sensitivity Figure 6-25 Time course of effects of drugs for depression. This figure depicts the different time courses for three effects of most drugs used to treat depression – namely, clinical changes, neurotransmitter (NT) changes, and receptor-sensitivity changes. Specifically, the amount of neurotransmitters changes relatively rapidly after a drug for depression is introduced. However, the clinical effect is delayed, as is the desensitization, or downregulation, of neurotransmitter receptors. This temporal correlation of clinical effects with changes in receptor sensitivity has given rise to the hypothesis that changes in neurotransmitter receptor sensitivity may actually mediate the clinical effects of drugs used for depression. These clinical effects include not only antidepressant and anxiolytic actions but also the development of tolerance to the acute side effects.

Chapter 6: Mood Disorders Figure 6-26 Neurotransmitter receptor hypothesis of antidepressant action. Although drugs for depression cause an immediate increase in monoamines, they do not have immediate therapeutic effects. This may be explained by the monoamine receptor hypothesis of depression, which states that depression is caused by upregulation of monoamine receptors; thus, clinical antidepressant effects would be related to downregulation of those receptors, as shown here. (A) When the monoamine reuptake pump is blocked, this causes more neurotransmitter (in this case, norepinephrine) to accumulate in the synapse. (B) The increased availability of neurotransmitter ultimately causes receptors to downregulate. The time course of receptor adaptation is consistent both with the delayed clinical effects of drugs for depression and with development of tolerance to side effects. A B Neurotransmitter Receptor Hypothesis of Antidepressant Action E E synaptogenesis monoamine Monoamine Signaling Increases BDNF Release, Which Modifies Monoamine Innervation neuroplasticity cell survival neurogenesis BDNF GE CaMK PKA CREB Figure 6-27 Monoamine signaling and brainderived neurotrophic factor (BDNF) release. The neuroprogression hypothesis of depression states that depression may be caused by reduced synthesis of proteins involved in neurogenesis and synaptic plasticity. BDNF promotes the growth and development of immature neurons, including monoaminergic neurons, enhances the survival and function of adult neurons, and helps maintain synaptic connections. Because BDNF is important for neuronal survival, decreased levels may contribute to cell atrophy. In some cases, low levels of BDNF may even cause cell loss. Monoamines can increase the availability of BDNF by initiating signal transduction cascades that lead to its release. Thus, increased synaptic availability of monoamines by reuptake inhibitors may lead to downstream increases in neurotrophic factors, a molecular effect that would correlate in timing with the clinical effects.

chronic clinical illness inflammation sleep early life adversity stress microbiome BDNF gene BDNF BDNF BDNF apoptosis Figure 6-28 Genetic and environmental factors may lead to loss of neurotrophic factors. Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) play a role in the proper growth and maintenance of neurons and neuronal connections. Multiple environmental factors, including chronic stress, inflammation, chronic illness, early life adversity, changes in the microbiome, and altered sleep could contribute to neuroprogression in depression by causing epigenetic changes that turn the genes for BDNF off, potentially reducing its production. Figure 6-29 Suppression of brainderived neurotrophic factor (BDNF) production. BDNF plays a role in the proper growth and maintenance of neurons and neuronal connections (right). If the genes for BDNF are turned off (left), the resultant decrease in BDNF could compromise the brain’s ability to create and maintain neurons and their connections. This could lead to loss of synapses or even whole neurons by apoptosis.

6 coronal plane normal depression coronal plane Figure 6-30 Loss of dendritic spines in depression. Reduction in neurotrophic factors compromises the maintenance of synaptic integrity and connectivity and can ultimately lead to synapse loss. This has been shown in structural magnetic resonance imaging studies of hippocampal volume, in which patients with depression have fewer

dendritic spines. inflammation Vulnerability to relapse Treatment resistance Functional brain abnormalities Structural brain abnormalities Damage to synapses and neurons Cognitive decline Symptomatic Brain Network Neuroprogression oxidative stress HPA dysregulation neurotrophic dysregulation epigenetic change Figure 6-31 Neuroprogression in depression is multifactorial. Neuroprogression in depression may be related to multiple factors that may themselves interact. Inflammation, oxidative stress, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may all contribute to neurotrophic dysregulation, which may lead to epigenetic changes, which may further exacerbate inflammation, oxidative stress, and HPA axis dysfunction. All these factors may ultimately contribute to damage to synapses and neurons, which may lead to both functional and structural brain abnormalities.

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Yet another factor potentially contributing to neurodegeneration in at least a subset of patients with depression is neuroinflammation (Figure 6-33). That is, a number of conditions and factors contribute to inflammation invading the central nervous system in a number of psychiatric disorders, maybe especially in depression (Figure 6-33). Those factors include not only chronic stress, but also obesity, early life/childhood adversity, disruption of the microbiome, and numerous chronic inflammatory medical illnesses (Figure 6-33A). In such patients, it is hypothesized that these factors activate microglia in the brain to release proinflammatory molecules (Figure 6-33B), which in turn attract immune cells such as monocytes and macrophages into the brain (Figure 6-33C) where they disrupt neurotransmission (Figure 6-33D), cause oxidative chemical stress, mitochondrial dysfunction, HPA-axis dysfunction, reduction of neurotrophic factor availability, and may contribute to neurodegeneration (Figures 6-31, 6-32A, and 6-32B). Neurons from the hippocampal area and amygdala normally suppress the HPA axis (Figure 6-32A), so if stress causes hippocampal and amygdala neurons to atrophy, with loss of their inhibitory input to the hypothalamus, this could lead to overactivity of the HPA axis (Figure 6-32B). In depression, abnormalities of the HPA axis have long been reported, including elevated glucocorticoid and insensitivity of the HPA axis to feedback inhibition (Figure 6-32B). Some evidence suggests that glucocorticoids at high levels could even be toxic to neurons and contribute to their atrophy under chronic stress (Figure 6-32B). Novel antidepressant treatments are in testing that target CRF (corticotropinreleasing factor) receptors, vasopressin 1B receptors, and glucocorticoid receptors (Figure 6-32B), in an attempt to halt and even reverse these HPA abnormalities in depression and other stress-related psychiatric illnesses. amygdala hippocampus ACTH glucocorticoids hypothalamus adrenal gland corticotropinreleasing factor pituitary The Hypothalamic-Pituitary-Adrenal (HPA) Axis Figure 6-32A Hypothalamic-pituitary-adrenal (HPA) axis. The normal stress response involves activation of the hypothalamus and a resultant increase in corticotropin-releasing factor (CRF), which in turn stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH causes glucocorticoid release from the adrenal gland, which feeds back to the hypothalamus and inhibits CRF release, terminating the stress response. The amygdala and hippocampus also provide input to the hypothalamus, to suppress activation of the HPA axis.

Chapter 6: Mood Disorders amygdala hippocampus ACTH glucocorticoids adrenal gland corticotropinreleasing factor glucocorticoid antagonist pituitary Hippocampal Atrophy and Hyperactive HPA in Depression CRF antagonist vasopressin 1B antagonist hypothalamus Figure 6-32B Hippocampal atrophy and hyperactive HPA axis in depression. In situations of chronic stress, hyperactivity of the HPA axis leads to excessive glucocorticoid release, which may eventually cause hippocampal atrophy. Because the hippocampus inhibits the HPA axis, atrophy in this region may lead to chronic activation of the HPA axis, which may increase risk of developing a psychiatric illness. Because the HPA axis is central to stress processing, it may be that novel targets for treating stress-induced disorders lie within the axis. Mechanisms being examined include antagonism of glucocorticoid receptors, corticotropin-releasing factor (CRF) receptors, and vasopressin 1B receptors. epigenetic changes to unwanted gene expression (Figure 6-31), leading ultimately to loss of synapses and death of neurons (Figure 6-31 and 6-33D). Another hypothesis for the neurobiological basis at least for some patients with depression is that it is a circadian rhythm disorder casing a phase delay in the sleep–wakefulness cycle (Figure 6-34). The degree of this phase delay correlates with the severity of depression. Numerous physiological measurements of circadian rhythms are also altered in depression, from flattening of the daily body-temperature cycle, elevation of cortisol secretion throughout the day, and also reducing melatonin secretion that also normally peaks at night and in the dark (Figure 6-35). Elevations of cortisol secretion and abnormalities of the HPA axis in depression are discussed above (Figures 6-32A and B). Other circadian rhythms that may be disrupted in depression include a reduction in BDNF and neurogenesis, also discussed above, and these normally peak at night. Desynchronization of biological processes can be so pervasive in depression that it is possible to characterize depression as fundamentally a circadian illness. It is possible, at least for some patients, that depression is due to a “broken” circadian clock. Numerous genes operate in a circadian manner, sensitive to light–dark rhythms and called clock genes. Abnormalities in various clock genes have been linked to mood disorders and for these patients with a circadian rhythm disorder (Figure 6-34), circadian rhythm treatments such as bright light (Figure 6-36A), melatonin (Figure 6-36B), phase advance, phase delay, and even sleep deprivation can have therapeutic effects. Not only do all of these various factors triggered by neuroinflammation, stress, genetics, and the environment (Figures 6-28, 6-30, 6-31, and 6-33) contribute to synaptic dysfunction and structural brain abnormalities with functional decline, theoretically they ultimately

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Major depressive episodes of course are named for their mood symptom of sadness and depression, and indeed sad mood has the strongest association with overall impairment of functioning, but the second strongest association with impaired overall functioning is cognitive symptoms, perhaps a bit surprising for something lead to at least three very unwanted clinical outcomes in depression: enduring cognitive decline increased vulnerability for further episodes of depression resistance to treatment with monoamine drugs for depression Blood monocyte macrophage activated microglia cytokines Brain Blood Chronic stress Chronic mental illness Obesity Microbiome Sleep A B monocyte macrophage resting microglia Genes Early life childhood adversity Brain Figure 6-33 Neuroinflammation in depression. Neurodegeneration in depression could be related to the development of neuroinflammation in some patients. (A) Chronic stress, obesity, early life adversity, disruption of the microbiome, chronic sleep issues, and chronic inflammatory diseases may all contribute to the development of neuroinflammation. Shown here are immune factors in the blood and resting microglia in the brain. (B) If microglia in the brain are activated due to chronic stress, obesity, etc., they can release proinflammatory cytokines.

Chapter 6: Mood Disorders Depressed patients with smaller hippocampal volumes have worse outcomes. A grim statistic is that memory in depression worsens as a function of the number of previous depressive episodes as though such episodes are damaging to the brain and the damage is cumulative. Interestingly, to support this haunting possibility is the observation that cognitive dysfunction in depression may be related to the number of past episodes of depression and to the duration of those episodes, and not to the called a “mood disorder” and not a “cognitive disorder.” Functional neuroimaging studies suggest that cognitive decline may manifest in the need for more effortful thinking because depressed patients show greater activation of brain regions involved in cognitive control, such as the dorsolateral prefrontal cortex and anterior cingulate cortex. Hippocampal decline in depression is discussed above and illustrated in Figure 6-30, and is correlated with duration of untreated depression. Blood Brain C D Blood Brain synaptic and neuronal damage Figure 6-33 (cont.) (C) Proinflammatory cytokines attract immune cells, such as monocytes and macrophages, into the brain. (D) Monocytes and macrophages can disrupt neurotransmission, cause oxidative stress and mitochondrial dysfunction, affect HPA-axis function, reduce availability of neurotrophic factors, and lead to epigenetic changes, which ultimately can lead to synaptic loss and neuronal death.

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Depression Causes Phase Delay in the Circadian Rhythms of Sleep-Wake Cycles “phase delay” Healthy Control Depression 7 am 7 am sleep sleep 11 pm Physiological Measurements of Circadian Rhythms Are Altered in Depression Body Temperature 37.2 37.0 (C) 36.8 36.6 36.4 Melatonin (pg/ml) Cortisol (ng/ml) 120 20 80 40 6 am 6 am 6 pm noon noon midnight severity of the symptoms in a current episode, again suggesting past damage. Cognitive symptoms are one of the most – if not the most – common residual symptom between depressive episodes once sadness and other symptoms recover. Thus, cognitive symptoms can endure longer than mood symptoms in major depressive disorder. How bad is the cognitive dysfunction? Some estimate that it is about the same degree of impairment as one has after a night of sleep deprivation, or after being legally intoxicated with alcohol, or after taking Figure 6-34 Depression can cause phase delay in circadian rhythms of sleep/wake cycles. Circadian rhythms describe events that occur on a 24-hour cycle. Many biological systems follow a circadian rhythm; in particular, circadian rhythms are key to the regulation of sleep/wake cycles. In patients with depression, the circadian rhythm is often “phase delayed,” which means that because wakefulness is not promoted in the morning, such patients tend to sleep later. They also have trouble falling asleep at night, which further promotes feelings of sleepiness during the day. 7 am 11 pm Figure 6-35 Physiological measurements of circadian rhythms are altered in some patients with depression. Circadian rhythms are evident in multiple biological functions, including body temperature, hormone levels, blood pressure, metabolism, cellular regeneration, sleep/wake cycles, and DNA transcription and translation. The internal coordination ordered by the circadian rhythm is essential to optimal health. In depression, there are altered physiological measurements of circadian rhythms, including less fluctuation in body temperature over the course of a 24-hour cycle, the same pattern but elevated cortisol levels over 24 hours, and the absence of a spike in melatonin levels at night. Healthy Control Depression a high dose of a benzodiazepine or antihistamine. Can you imagine living all day long, every day, with this degree of cognitive impairment? Cognitive dysfunction of this degree is not specific for patients with depression, but is very common across many psychiatric disorders, from unipolar to bipolar disorder, schizophrenia, anxiety/trauma/impulsive disorders, ADHD (attention deficit hyperactivity disorder), and beyond. Targeting cognitive symptoms with current treatments across psychiatric disorders is therefore an important therapeutic strategy, and

6 Figure 6-36A The setting of circadian rhythms, part 1. Although various factors can affect the setting of circadian rhythms, light is the most powerful synchronizer. When light enters through the eye it is translated via the retinohypothalamic tract to the suprachiasmatic nucleus (SCN) within the hypothalamus. The SCN, in turn, signals the pineal gland to turn off melatonin production. For individuals with depression who have dysregulation of circadian rhythms, bright-light therapy in the early morning may help to reset the circadian rhythm. SCN retinohypothalamic tract pineal gland Figure 6-36B Melatonin and circadian rhythms. During darkness, there is no input from the retinohypothalamic tract to the suprachiasmatic nucleus (SCN) within the hypothalamus. Thus, darkness signals the pineal gland to produce melatonin. Melatonin, in turn, can act on the SCN to reset circadian rhythms. For individuals with depression who have dysregulated circadian rhythms, melatonin in the early evening may help to reset the circadian rhythm. melatonin SCN retinohypothalamic tract pineal gland

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY a critical need for better drugs for cognition exists. In the meantime, perhaps the best chance to prevent adverse cognitive and functional outcomes in depression is to treat early and completely, whenever possible. Changes in structural and functional outcomes in depression in fact may be potentially reversible when captured at the stage of loss of synapses without loss of neurons, and that is what rapid-acting drugs for depression, which act on glutamate and GABA systems, hold promise for doing: namely, triggering the formation of new synapses. These drugs are discussed in Chapter 7. Here we will just mention that downstream improvement in neuroplasticity may be possible for monoaminetargeting drugs when those drugs are effective. More recently it has been discovered that improvements in animal models of neuroplasticity can be observed after boosting glutamatergic neurotransmission with novel drugs for depression (Figure 6-37). It is possible that this Downstream Improvement in Neuroplasticity with Novel Drugs for Depression Monoamine regulation Glutamate regulation GABA regulation DA 5HT NE Signaling cascades MAPK RSK cAMP PKC GSK-3 CaMK Wnt/Frz Activation of cAMP response element binding protein (CREB) Genes turned on BDNF BDNF Increased expression of AMPA receptor subunits Downregulation of NMDA receptors Increased neuroplasticity and restored neurotransmission may also be occurring with the novel GABAergic drugs currently being developed. If so, these newer agents have the potential for rapid onset of an antidepressant effect since their molecular effects (Figure 6-37) can reverse synaptic loss and show new synapse formation within minutes to hours (reversal of synapse loss is shown in depression in Figure 6-30; see also Chapter 7). It is also possible that agents targeting glutamate, GABA, and other non-monoaminergic targets will hold promise for treating patients who do not respond to monoaminergic therapeutics. Restoration of neurotransmitterrelated signal transduction cascades by drugs of any mechanism that can successfully treat depression can also hypothetically increase BDNF and other trophic factors and therefore potentially restore lost synapses. In some brain areas, such as the hippocampus, not only can synapses potentially be restored, but it is possible that some lost neurons might even be replaced by neurogenesis. Figure 6-37 Downstream effects on neuroplasticity. In depression, there may be a deficiency in downstream signal transduction, leading to reduced synthesis of proteins involved in neurogenesis and synaptic plasticity, such as brain-derived neurotrophic factor (BDNF). Treatment with drugs for depression, both traditional monoamine reuptake inhibitors as well as novel agents that affect glutamate or GABA, can stimulate a variety of signaling cascades. Each of the signaling cascades depicted is capable of activating cAMP response element binding protein (CREB), which can elicit the expression of numerous genes involved in neuroplasticity, including BDNF. Another form of synaptic plasticity, long-term potentiation (LTP), involves the strengthening of synapses through the modulation of glutamate receptors. The activation of CREB increases the expression of α-amino-3-hydroxy-5-methyl-4isoxazole-propionic acid (AMPA) receptor subunits and downregulates N-methyl-D-aspartate (NMDA) receptors. Modifying the AMPA:NMDA receptor ratio by increasing AMPA while reducing NMDA input may restore glutamate homeostasis and facilitate neuroplasticity in the depressed brain. BDNF BDNF Increased proteins involved in neuroplasticity

SYMPTOMS AND CIRCUITS IN MOOD DISORDERS Currently, a major hypothesis in psychiatry is that psychiatric symptoms are linked to inefficient information processing in specific brain circuits, with different circuits mediating different symptoms according to an evolving understanding of the topographical distribution of different functions across different brain regions, sometimes called nodes, and across different brain circuits, with connections forming networks. If possibly reductionistic and oversimplified, the theoretical notion is to associate specific nodes in the network with specific psychiatric symptoms. Here we will discuss how this idea might apply to doing this for the nine symptoms of a major depressive episode (Figure 6-1) and the nine symptoms of a manic episode (Figure 6-2). Why do this if our information is still incomplete and evolving about domains of psychopathology and the circuits underlying them? It is because it helps us better understand the presenting symptoms of our patients as well as their symptoms that persist after treatment. The goal of this approach is to have a strategy for relieving all symptoms in order to get to complete remission, and to do so as rationally as possible based upon how those specific circuits are currently thought to be regulated by neurotransmitters in normal functioning and in Match Each Diagnostic Symptom for a Major Depressive Episode to Hypothetically Malfunctioning Brain Circuits psychomotor fatigue (physical) pleasure interests fatigue/ energy concentration interest/pleasure psychomotor fatigue (mental) PFC S NA BF T guilt suicidality worthlessness Hy NT A H mood guilt suicidality worthlessness mood sleep appetite Chapter 6: Mood Disorders psychiatric disorders. That strategy also involves rational use of the available drugs that are known to target the regulation of those same neurotransmitters, and, therefore, to target improvement of the symptoms those neurotransmitters regulate. Let’s now explain how this strategy works. Each of the nine symptoms listed for the diagnosis of a major depressive episode can be mapped onto brain circuits whose inefficient information processing theoretically mediates these symptoms (compare Figure 6-1 and Figure 6-38). Each of the symptoms listed for the diagnosis of a manic episode can similarly be mapped onto some of these same but also some different brain circuits (compare Figure 6-2 and 6-39). Note the innervation of these various brain areas by the three monoamine neurotransmitter systems (Figure 6-40). Glutamate and GABA are ubiquitous throughout essentially every area of the brain. This pattern of monoamine innervation provides the opportunity to target various neurotransmitters in order to improve the efficiency of information processing in these brain areas, and thus, reduce symptoms. Each node in the networks regulating psychiatric symptoms has neurotransmitters distributed to it in a unique if partially overlapping pattern that regulates each specific hypothetically malfunctioning brain region (see Figures 6-38 through 6-40). Targeting each region with drugs which act on Figure 6-38 Matching depression symptoms to circuits. Alterations in neuronal activity and in the efficiency of information processing within each of the brain regions shown here can lead to symptoms of a major depressive episode. Functionality in each brain region is hypothetically associated with a different constellation of symptoms. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; Hy, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum. C psychomotor SC fatigue (physical) 277

Match Each Diagnostic Symptom for a Manic Episode to Hypothetically Malfunctioning Brain Circuits motor/agitation racing thoughts goal-directed grandiosity racing thoughts grandiosity distractibility talkative/pressured speech PFC S NA BF T decreased sleep/arousal Hy NT mood A H risks grandiosity talkative/pressured speech racing thoughts mood decreased sleep/arousal the relevant neurotransmitters that regulate those brain regions potentially leads to reduction of each individual symptom. The idea is that whenever adjustment of specific neurotransmitter-mediated neurotransmission can enhance the efficiency of information processing in the hypothetically malfunctioning circuits for each specific symptom, it will relieve that symptom. If successful, this targeting of neurotransmitters in specific brain areas could even eliminate all symptoms and cause a major depressive episode to go into remission. Many of the mood-related symptoms of depression can be categorized as having either too little positive affect or too much negative affect (Figure 6-41). This idea is linked to the fact that there are diffuse anatomic connections of monoamines throughout the brain, with diffuse dopamine dysfunction in this system driving predominantly the reduction of positive affect, diffuse serotonin dysfunction driving predominantly the increase in negative affect, and norepinephrine dysfunction being involved in both. Thus, reduced positive affect includes such symptoms as depressed mood but also loss of happiness, joy, interest, pleasure, alertness, energy, enthusiasm, and self-confidence (Figure 6-41, left). Enhancing dopamine function and possibly also norepinephrine function may improve information processing in the circuits mediating this cluster of symptoms. On the other hand, increased negative affect includes not only depressed mood but guilt, disgust, Figure 6-39 Matching mania symptoms to circuits. Alterations in neurotransmission within each of the brain regions shown here can be hypothetically linked to the various symptoms of a manic episode. Functionality in each brain region may be associated with a different constellation of symptoms. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; Hy, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum. decreased sleep/arousal C SC fear, anxiety, hostility, irritability, and loneliness (Figure 6-41, right). Enhancing serotonin function, and possibly also norepinephrine function, may improve information processing in the circuits that hypothetically mediate this cluster of symptoms. For patients with symptoms of both clusters, they may require triple-action treatments that boost all three of the monoamines. The same general paradigm of neurotransmitter regulation of the efficiency of information processing in specific brain circuits can be applied to mania and to mixed states as well as depression. Although a simplistic notion is that the circuit problem in mania may be the opposite of that for depression, namely too much in mania versus too little neurotransmitter and neuronal activity in depression, the reality is that you can have manic and depressive symptoms at the same time, and can traverse the entire mood spectrum from full depression, with increasing amounts of mania, until arriving at pure mania (Figure 6-7). A more sophisticated and modern notion of mood disorder is that neuronal transmission in inefficient brain circuits may be chaotic and not just too high or too low. The illustrations drawn in this chapter sometimes imply there is a single neuron going from one node to another in the network (see for example Figure 6-40), but the reality is that each node in the network is connected by a vast bundle of neurons, and not all of them are hypothetically functioning the same way in a mood disorder. Some may have

PFC S NA BF T Hy C A NT H A SC PFC S NA BF T Hy C NT A H SC B PFC S NA BF T Hy C NT A H SC C neurotransmission that is perhaps up, others down, others normal, and still others vacillating chaotically from up to down in activity. No wonder a patient can appear to have varying symptoms of concomitant mania during a full depressive episode, not only from one episode to the Chapter 6: Mood Disorders Figure 6-40 Major monoamine projections. (A) Dopamine has widespread ascending projections that originate predominantly in the brainstem (particularly the ventral tegmental area and substantia nigra) and extend via the hypothalamus to the prefrontal cortex, basal forebrain, striatum, nucleus accumbens, and other regions. Dopaminergic neurotransmission is associated with movement, pleasure and reward, cognition, psychosis, and other functions. In addition, there are direct projections from other sites to the thalamus, creating the “thalamic dopamine system,” which may be involved in arousal and sleep. (B) Norepinephrine has both ascending and descending projections. Ascending noradrenergic projections originate mainly in the locus coeruleus of the brainstem; they extend to multiple brain regions, as shown here, and regulate mood, arousal, cognition, and other functions. Descending noradrenergic projections extend down the spinal cord and regulate pain pathways. (C) Like norepinephrine, serotonin has both ascending and descending projections. Ascending serotonergic projections originate mainly in the raphe nucleus in the brainstem and extend to many of the same regions as noradrenergic projections. These ascending projections may regulate mood, anxiety, sleep, and other functions. Descending serotonergic projections extend down the brainstem and through the spinal cord; they may regulate pain. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; Hy, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum. next, but even within an episode over time. This situation presents a challenge to find treatments that can stabilize rather than simply increase or reduce neurotransmitter action. Treatments for mood disorders are discussed in detail in Chapter 7. Symptom-Based Treatment Selections The neurobiologically informed psychopharmacologist may opt for a symptom-based approach to selecting or combining a series of drugs for treatment of depression, mania, and mixed states (Figures 6-42 through 6-44). This strategy leads to the construction of a portfolio of multiple psychopharmacological mechanisms in order to treat all residual symptoms of a mood disorder until the patient achieves sustained remission. Specific drugs and treatment choices are discussed in Chapter 7. Here we cover the rationale for thinking in neurobiological terms, namely, the anatomy of brain circuits regulating specific symptoms (Figures 6-38 and 6-39) and the neurotransmitters that regulate the circuits (Figure 6-40). The purpose of this approach is to apply understanding of how a given drug works on neurotransmitters, so a clinician can make rational treatment choices. Using this approach, those treatment choices are based upon addressing those specific symptoms of a given patient by targeting the unique collection of hypothetically malfunctioning brain circuits. This “tailored” approach 279

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY depressed mood loss of happiness

(joy) loss of interest/pleasure loss of energy/enthusiasm decreased alertness decreased self-confidence reduced positive affect + +++ + increased negative affect normal mood DA dysfunction NE dysfunction NE dysfunction 5HT dysfunction depressed mood guilt/disgust fear/anxiety hostility irritability loneliness

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5HT NE DA NE Figure 6-41 Positive and negative affect. Mood-related symptoms of depression can be characterized by their affective expression – that is, whether they cause a reduction in positive affect or an increase in negative affect. Symptoms related to reduced positive affect include depressed mood; loss of happiness, interest, or pleasure; loss of energy or enthusiasm; decreased alertness; and decreased selfconfidence. Reduced positive affect may be hypothetically related to dopaminergic dysfunction, with a possible role of noradrenergic dysfunction as well. Symptoms associated with increased negative affect include depressed mood, guilt, disgust, fear, anxiety, hostility, irritability, and loneliness. Increased negative affect may be linked hypothetically to serotonergic dysfunction and perhaps also noradrenergic dysfunction. depressed mood concentration fatigue major depressive disorder psychomotor guilt/ worthlessness appetite/ weight sleep suicidality interest/ pleasure Symptom-Based Algorithm for Treating Depression Part One: Deconstructing Most Common Residual Diagnostic Symptoms Figure 6-42 Symptom-based algorithm for treating depression, part 1. Shown here is the diagnosis of major depressive disorder deconstructed into its symptoms (as defined by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition [DSM-5]). Of these, sleep disturbances, problems concentrating, and fatigue are the most common residual symptoms.

attempts to address the individual patient's needs and thereby provide relief of the specific symptoms of that individual patient rather than treating all patients with a given diagnosis the same. How is this approach implemented? First, symptoms are evaluated and a diagnosis constructed by putting them all together, but then that diagnosis is deconstructed into Symptom-Based Algorithm for Treating Depression Part Two: Match Most Common Residual Symptoms to Hypothetically Malfunctioning Brain Circuits interests fatigue/energy fatigue (physical) concentration interest fatigue (mental) PFC S NA Hy insomnia Symptom-Based Algorithm for Treating Depression Part Three: Target Regulatory Neurotransmitters with Selected Pharmacological Mechanisms fatigue NE/DA concentration NE/DA sleep Boost NE or DA 5HT/GABA/ histamine Boost GABA Block 5HT, HA Chapter 6: Mood Disorders a list of specific symptoms that the individual patient is experiencing (Figure 6-42). Next, these symptoms are matched with the brain circuits that hypothetically mediate these symptoms (Figure 6-43) and then with the known neuropharmacological regulation of these circuits by neurotransmitters (Figure 6-44). Finally, available treatment options that target these neuropharmacological Figure 6-43 Symptom-based algorithm for treating depression, part 2. In this figure the most common residual symptoms of major depression are linked to hypothetically malfunctioning brain circuits. Insomnia maybe linked to the hypothalamus (Hy), problems concentrating to the dorsolateral prefrontal cortex (PFC), reduced interest to the PFC and nucleus accumbens (NA), and fatigue to the PFC, striatum (S), NA, and spinal cord (SC). SC fatigue (physical) Figure 6-44 Symptom-based algorithm for treating depression, part 3. Residual symptoms of depression can be linked to the neurotransmitters that regulate them and then, in turn, to pharmacological mechanisms. Fatigue and concentration are regulated in large part by norepinephrine (NE) and dopamine (DA), and therefore may be treated by agents that boost NE and/ or DA. Sleep disturbance is regulated by serotonin (5HT), γ-aminobutyric acid (GABA), and histamine (HA) and can be treated with agents that boost GABA or block 5HT or HA. 281

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY mechanisms are chosen to eliminate symptoms one by one (Figure 6-44). When symptoms persist despite treatment, another treatment with a different mechanism is added or switched. No evidence proves that this is a superior approach, but it appeals not only to clinical intuition but also to neurobiological reasoning as well as to the goal of individualizing psychopharmacological treatment rather than treating all patients with the same diagnosis the same way in the hope that this will lead to a better outcome. For example, for the symptoms of "problems concentrating" and "fatigue," this approach suggests targeting both NE and DA (Figure 6-44). This can also call for stopping the use of a serotonergic medication if this is partially the cause of these symptoms. On the other hand, for "insomnia," this symptom is hypothetically associated with an entirely different malfunctioning circuit regulated by different neurotransmitters (Figure 6-43); therefore, the treatments for this symptom call for a different approach, namely the use of agents that act on the GABA system or that work to block rather than boost the serotonin or histamine system (Figure 6-44). It is possible that any of the symptoms shown in Figure 6-44 would respond to whatever drug is administered, but this symptom-based approach can tailor the treatment portfolio to each individual patient, possibly finding a faster way of reducing specific symptoms with more tolerable treatment selections for that patient than a purely random approach. The symptom-based approach for selecting treatments for depression can also be applied to treating common associated symptoms of depression that are not components of the formal diagnostic criteria, such as anxiety and pain. Sometimes it is said that for a good clinician to get patients into remission, it requires targeting at least a dozen of the nine symptoms of a mood disorder! Fortunately, psychiatric drug treatments do not respect psychiatric disorders. Treatments that target pharmacological mechanisms in specific brain circuits do so no matter what psychiatric disorder is associated with the symptom linked to that circuit. Thus, symptoms of one psychiatric disorder may be treatable with a proven agent that is known to treat the same symptom in another psychiatric disorder. For example, anxiety can be reduced in patients with major depression who do not have a full-criteria anxiety disorder with the same serotonin and GABA mechanisms proven to work in anxiety disorders (see Chapter 8 on anxiety disorders and their treatments). Painful physical symptoms can be treated with serotonin–norepinephrine reuptake inhibitors (SNRIs) and other approaches (see Chapter 9 on chronic pain and its treatment). In conclusion, the symptom-based algorithm for selecting and combining treatments of mood disorders, and using them to build a portfolio of mechanisms until each symptom of a mood disorder is abolished, is the modern psychopharmacologist’s approach to mental illnesses in general and to mood disorders in particular. This approach follows contemporary notions of neurobiological disease and drug mechanisms, with the goal of treatment being sustained remission. SUMMARY This chapter has described the mood disorders across a spectrum from depression to mania with many mixed states in between. For prognostic and treatment considerations, it is important not only to distinguish unipolar depression from bipolar depression, but also to detect mixed states of subsyndromal mania or depression whenever they exist. Although mood disorders are indeed disorders of mood, they are much more, and several different symptoms in addition to a mood symptom are required to make a diagnosis of a major depressive episode or a manic episode. The classic monoamine hypothesis of depression, suggesting that dysfunction of one or more of the three monoamines dopamine, norepinephrine, or serotonin, or their receptors, may be linked to symptoms in major depression, has been updated and expanded to include the notion of abnormalities in neurotrophic factors, sleep, circadian rhythms, neuroinflammation, stress, genes, and the environment in the complex etiology of mood disorders. Also discussed is the troubling notion that mood disorders may be progressive, especially if not adequately treated. Finally, each symptom of a mood disorder can be matched to a hypothetically malfunctioning neuronal circuit. Targeting one or more of the neurotransmitters in specific brain regions may improve the efficiency of information processing there and reduce the symptom caused by that area’s malfunctioning. Other brain areas associated with the symptoms of a manic episode can similarly be mapped to various hypothetically malfunctioning brain circuits. Understanding the localization of symptoms in circuits, as well as the neurotransmitters that regulate these circuits in different brain regions, can set the stage for choosing and combining treatments for each individual symptom of a mood disorder, with the goal being to reduce all symptoms and lead to remission.

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