Classification and Symptoms of Mood Disorders and Disease Models of Depressive Disorders

Mood disorders are often referred to as affective disorders. Affect is the external display of emotion, while emotion that is felt internally is referred to as mood. Disorders of mood consist of a variety of symptoms that extend beyond disruption of mood. The most effective clinical approach to treatment is to first construct a diagnosis from an individual patient's symptoms profile, and then deconstruct its component symptoms so that each symptom can be addressed individually as a therapeutic target. A neurobiological approach to treatment begins with matching each symptom to its hypothetically malfunctioning brain circuit, regulated by one or more neurotransmitters. Drug selection should then target specific neurotransmitters in the symptomatic brain circuits in the individual patient. Targeting these malfunctioning circuits and improving neural processing should result in reduced symptoms.

Traditionally, mood symptoms of mania and depression have been considered as being "poles" apart. Patients who experience just the down or depressive pole are classified as having unipolar depression. Patients who at different times experience the up (mania or hypomania) pole and the down pole (depressive pole) are classified as having bipolar disorder. Bipolar I disorder is characterized by full-blown manic episodes typically followed by depressive episodes. Bipolar II disorder is characterized by at least one hypomanic episode and one major depressive episode. Finally, depression and mania may even occur simultaneously, which is classified as a "mixed" mood state or "mixed features" according to the *Diagnostic and Statistical Manual of Mental Disorders Fifth Ed. Text Revision (DSM-5-TR)*. The introduction of the mixed features modifier has moved the field away from considering depression and mania as distinct categories and towards the concept that they are opposite ends of the spectrum.

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The Mood Disorder Spectrum

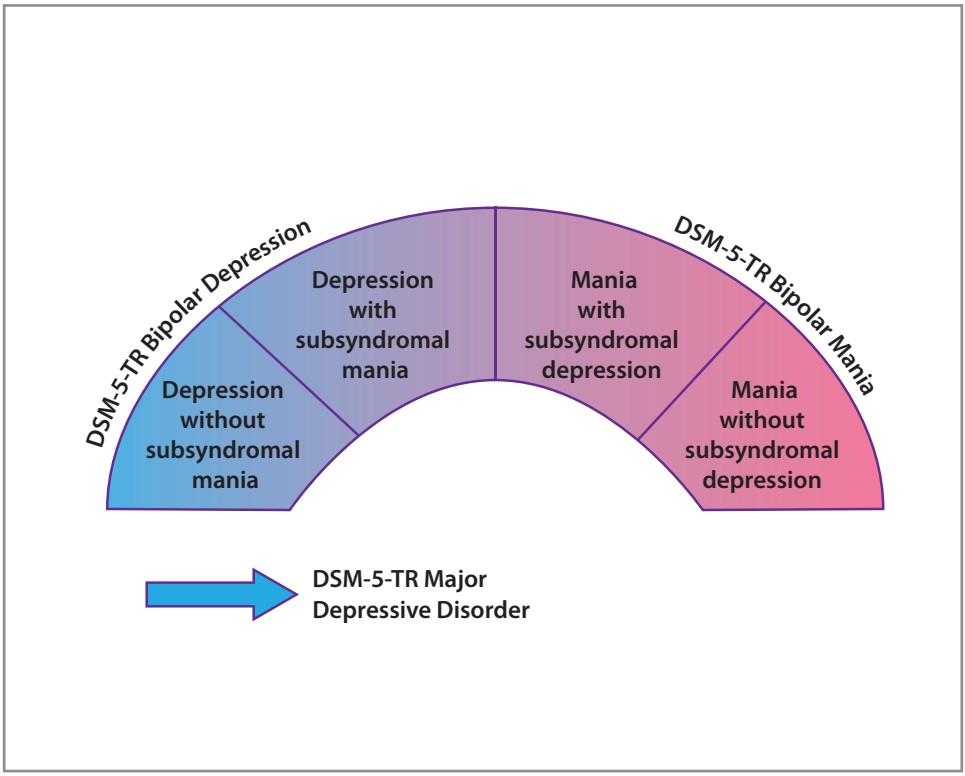

FIGURE 1.1. The field has moved away from characterizing depression and mania as distinct categories and now views them as opposite ends of a spectrum, with varying degrees of either or both between. Many patients are not purely manic or depressed, but rather they experience a mixture of symptoms. The specific mix of mood symptoms may change along the mood spectrum over the course of the illness (Stahl, 2021).

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Description of Depressive State Symptoms in Mood Disorders

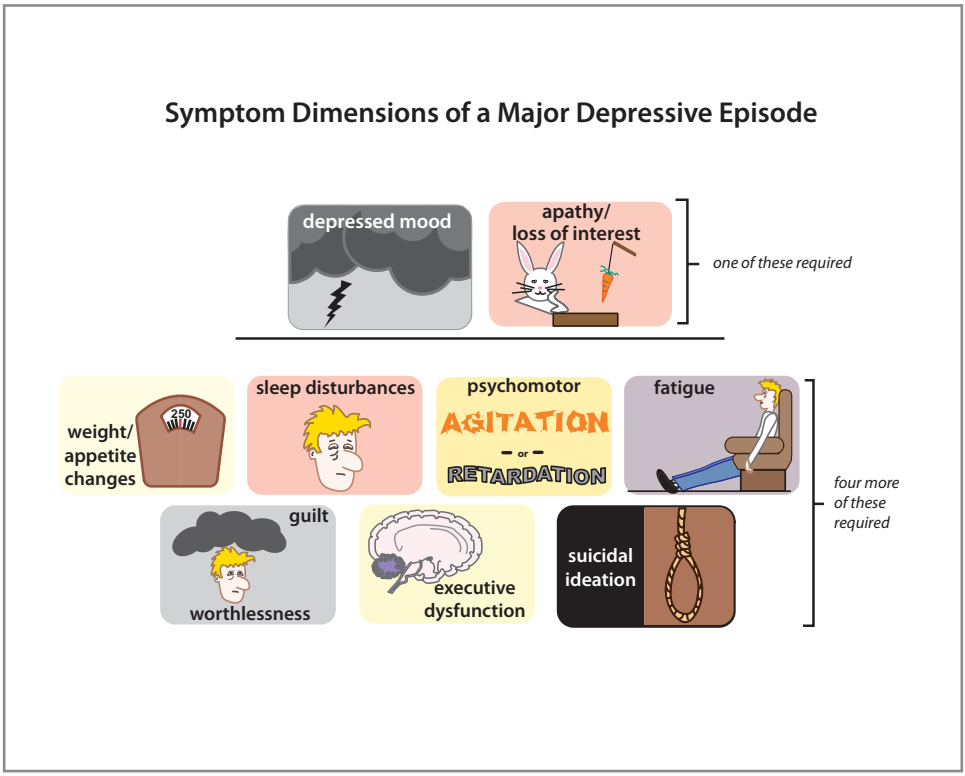

FIGURE 1.2. According to the DSM-5-TR (American Psychiatric Association, 2022), a major depressive episode is characterized by either depressed mood or loss of interest and at least four of the following: fatigue, insomnia/hypersomnia, weight/appetite alterations, fatigue, psychomotor agitation/retardation, feelings of guilt or worthlessness, executive dysfunction, and suicidal ideation (Stahl, 2021).

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Description of Manic State Symptoms in Mood Disorders

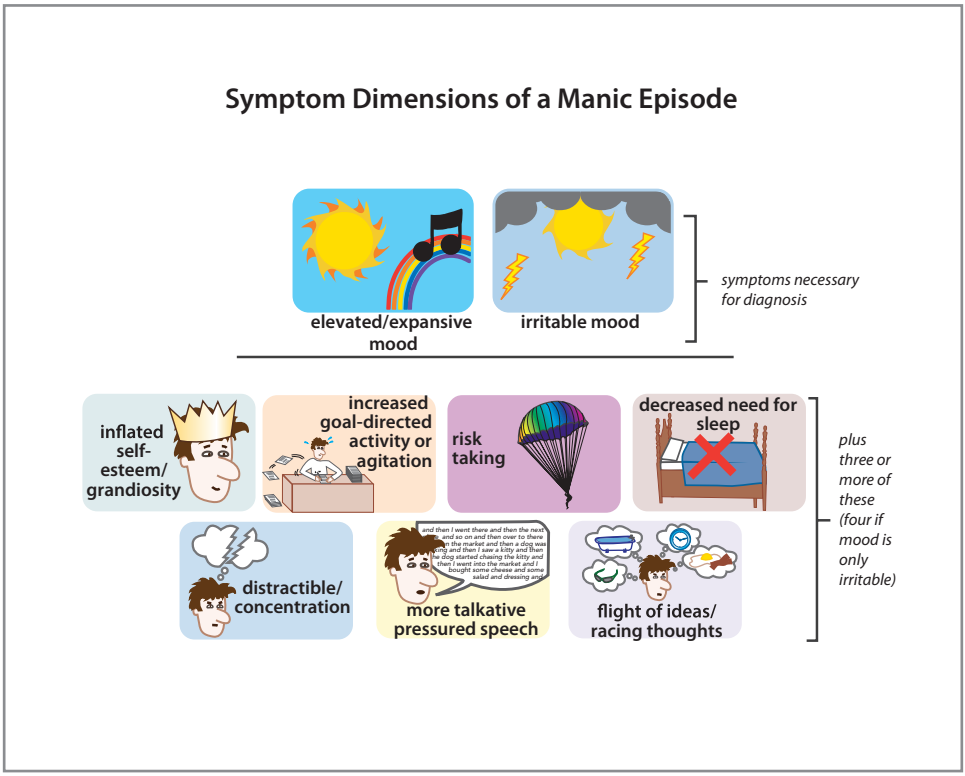

FIGURE 1.3. According to the DSM-5-TR, a manic episode consists of either expansive/elevated mood or irritable mood and at least three of the following (four if mood is irritable): increased goal-directed activity or agitation, inflated self-esteem/grandiosity, decreased need for sleep, risk taking, distractibility, racing thoughts, and pressured speech (Stahl, 2021).

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The Spectrum of Mood Disorder Symptoms

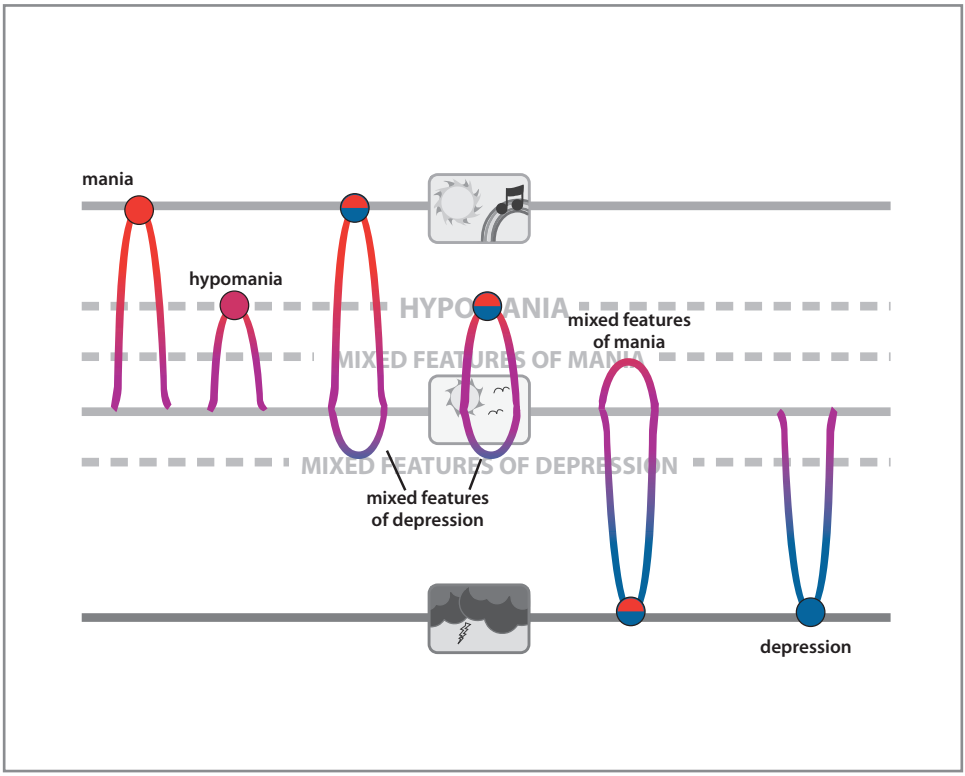

FIGURE 1.4. Mood disorder symptoms occur along a spectrum, with the polar ends consisting of pure mania or hypomania (the "up" pole) and pure depression (the "down" pole). Patients can also experience simultaneous symptoms of both poles. This is referred to as mania/hypomania with mixed features of depression, or depression with mixed features of mania. Patients may experience any combination of these symptoms over the course of the illness. Subsyndromal manic or depressive episodes may also occur, in which case there are not enough symptoms or the symptoms are not severe enough to fit the diagnostic criteria for one of these episodes. The presentation of mood disorders can vary widely, both between individuals and within the individual patient (Stahl, 2021).

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Mixed Features 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)

FIGURE 1.5. When screening for mania/hypomania with mixed features, the patient's symptoms must meet the full criteria for mania and at least three of the depressive symptoms listed in this chart. When screening for depression with mixed features, the symptoms must meet full criteria for a depressive episode, along with at least three of the manic/hypomanic symptoms listed in this chart. When screening for depression with mixed features, assessing whether there is a family history of mania or hypomania should be highly prioritized (Stahl, 2021; Stahl and Morrisette, 2019).

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Identifying Depression Within the Mood Disorder Spectrum

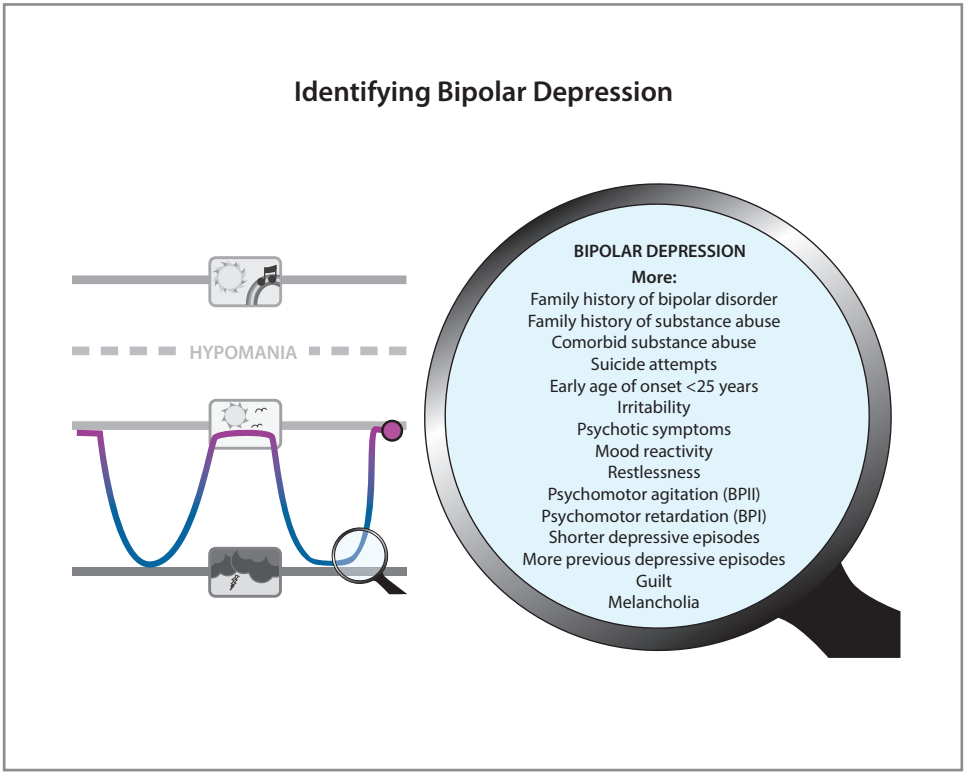

FIGURE 1.6. Aside from a history of prior manic/hypomanic episodes, patients with bipolar depression are diagnosed with identical criteria as patients with unipolar depression. While they may have similar symptoms, the long-term outcomes differ between patients with bipolar depression versus unipolar depression, thus treatment approaches are different. The wrong treatment approach could have debilitating effects on the patient's quality of life and missed or delayed diagnosis is common. Over one-third of patients with unipolar depression are subsequently re-diagnosed with bipolar disorder and up to 60% of depressed patients with bipolar II disorder are initially diagnosed with unipolar depression. Reasons for missed or delayed diagnosis may be that the patient has either not experienced mania/hypomania yet or that prior occurrence was missed at screening (Stahl, 2021).

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Distinguishing Unipolar Depression From Bipolar Depression

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 underreport them.

FIGURE 1.7. While it is important to distinguish bipolar depression from unipolar depression, it can be challenging while the patient is in the depressed state. There are two main questions that can help to determine whether a patient is unipolar or bipolar: "Who's your daddy?" and "Where's your mama?" The first question, "Who's your daddy?" equates to taking a family history. A first-degree relative with a bipolar spectrum disorder increases the chance that the patient has bipolar depression versus unipolar depression, and it is arguably the most robust and reliable risk factor for bipolar depression. The second question "Where's your mama?" equates to collecting additional history from someone who is close to the patient (e.g., roommate, caretaker, spouse, family member). This question is important because many patients with bipolar depression underreport their manic symptoms (Stahl, 2021). ECT, electroconvulsive therapy.

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Is Major Depressive Disorder Progressive?

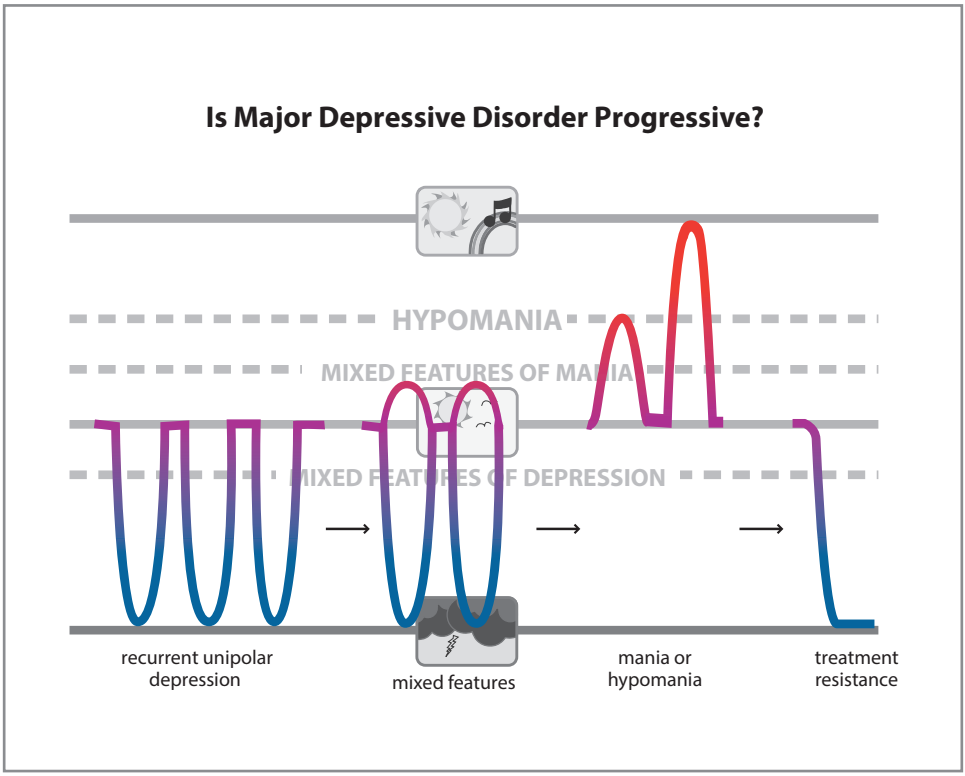

FIGURE 1.8. There is evidence that mood disorders may be progressive. While screening and monitoring patients with mood disorders it is essential to look for mixed features in depressed patients, whether they have unipolar or bipolar depression. There is evidence that unipolar depression can progress to mixed features, mixed features can progress to bipolar disorder, and bipolar disorder can progress to treatment resistance. Even subthreshold manic symptoms are strongly associated with conversion to bipolar disorder, with each manic symptom increasing the risk by 30%. Approximately one-quarter of adult patients with unipolar depression and about one-third of all patients with bipolar I or II depression have subsyndromal symptoms of mania, and there are even higher estimates of mixed features in children and adolescents with unipolar depression. Early detection and treatment of all symptoms, whether manic or depressive, may prevent the progression of the mood disorder (Fiedorowicz et al., 2011).

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Evolving Disease Models in Depressive Disorders

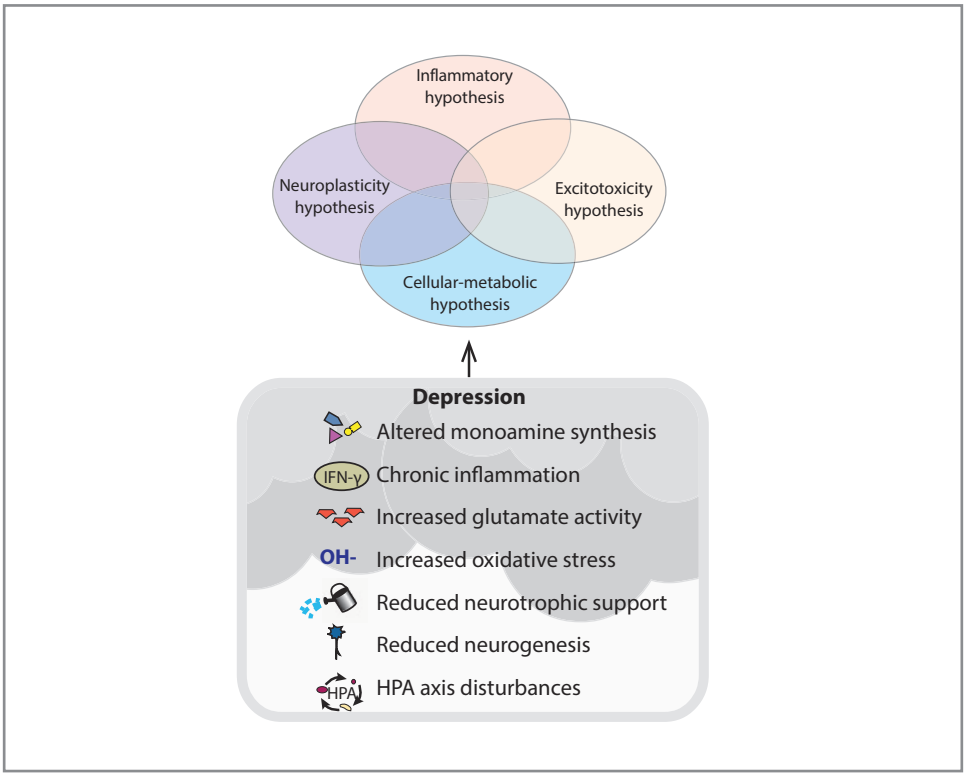

FIGURE 1.9. There is a growing body of research on the pathogenesis of depression identifying interactions between multiple biological systems. The major disease models are centered around altered monoamine functioning, chronic inflammation, excitotoxicity, neurogenesis and neuroplasticity disruptions/reduced neurotrophic support, endocrine problems, and cellular-metabolic factors (Dowlati et al., 2010; Howren et al., 2009; Miller et al., 2009; Pace et al., 2007; Pariante, 2009). As our understanding grows about the integration of these models, and how they are influenced by external/environmental factors, the more useful they will become to the screening and treatment of depressive disorders. It is important to remember that multiple components from these various models may be contributing to depressive symptoms and thus should be factored into the treatment plan for each individual patient. HPA, hypothalamic-pituitary-adrenal.

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Early Disease Model in Depression: Monoamine Hypothesis

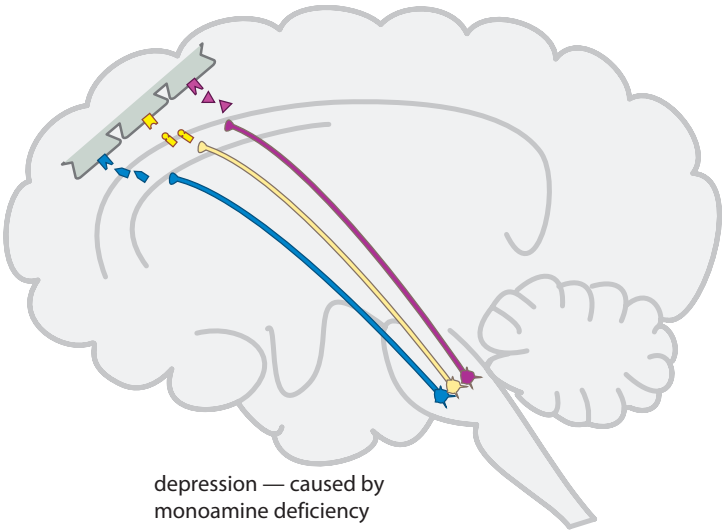

FIGURE 1.10. The classic neurobiological theory about the etiology of depression proposes that depressive disorders are caused by a deficiency of monoamine neurotransmission. It hypothesizes that the opposite, an excess of monoamine neurotransmission, causes mania. While mood disorders often involve dysfunction of one or more of these three monoamine systems (dopamine, serotonin, and norepinephrine), this "chemical imbalance" theory is now considered outdated and inaccurate, considering the lack of direct evidence to support it (Kohler et al., 2016; Stahl, 2021).

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The Monoamine Receptor Hypothesis and Neurotrophic Factors

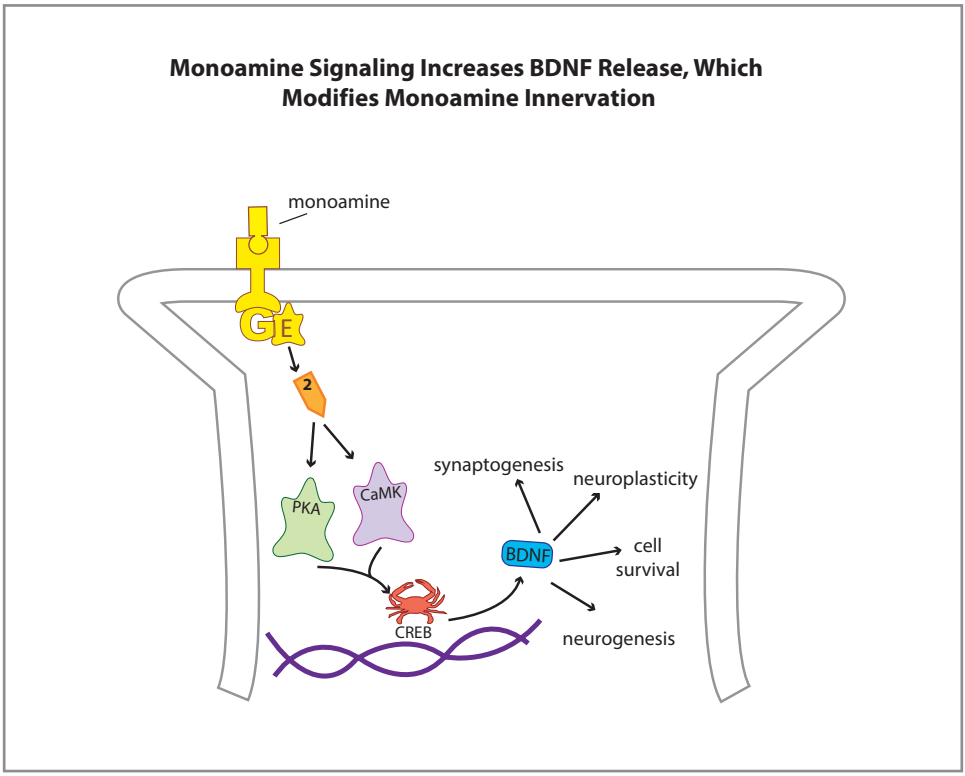

FIGURE 1.11. While classic antidepressants result in increased levels of monoamines almost immediately after administration, the clinical improvement in depressive symptoms is not observed for weeks. Improved symptoms instead seem to correspond with downstream synthesis of growth factors such as brain-derived neurotrophic factor (BDNF). BDNF promotes the growth and development of young neurons, including monoaminergic neurons. It also enhances the survival of adult neurons and increases synaptogenesis. Monoamines can increase BDNF levels by initiating signal transduction cascades that result in its release. Thus, increased levels of monoamines that result from monoamine reuptake inhibitors may lead to downstream increases in neurotrophic factors, which correlates with the timeline of clinical improvement (Grady and Stahl, 2015; Stahl, 2021).

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Beyond Monoamines: The Neuroplasticity Hypothesis of Depression

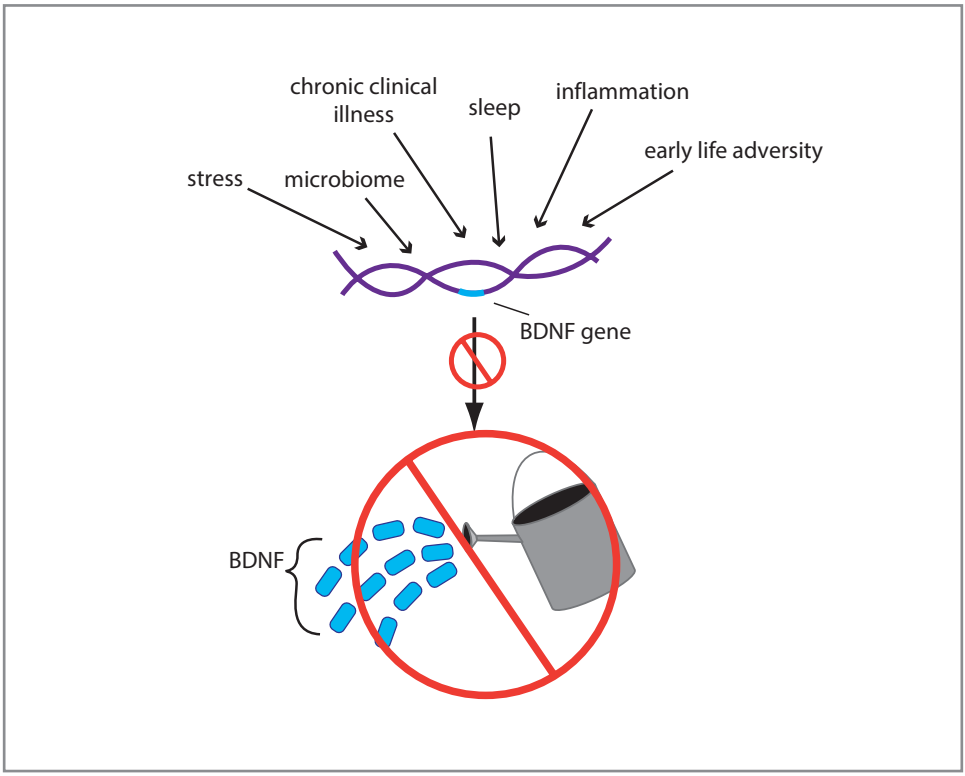

FIGURE 1.12. Environmental and genetic factors such as chronic illness, early life adversity, and alterations in the microbiome, stress, altered sleep, and inflammation may lead to the loss of growth factors, such as BDNF. Neurotrophic factors like BDNF are important to neuronal growth and survival, neuronal connections, and ultimately neuroplasticity. Genetic and environmental factors may contribute to neuroprogression in depression by resulting in epigenetic alterations that turn off genes for BDNF, reducing its production (Grady and Stahl, 2015; Stahl, 2021).

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The Neuroprogression Hypothesis of Depression: Suppressed Brain-Derived Neurotrophic Factor

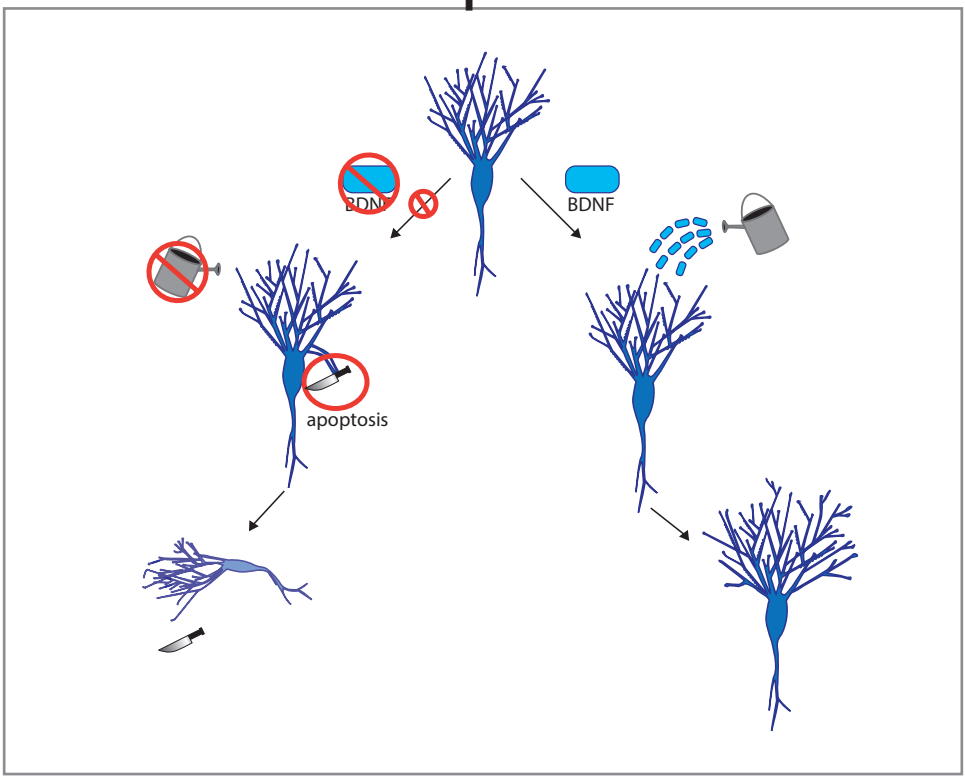

FIGURE 1.13. Suppression of BDNF results in a lack of synaptic maintenance, which in turn leads to a loss of synapses and dendritic arborization, ultimately resulting in apoptosis, or neuron cell death. This has been observed in structural magnetic resonance imaging studies of hippocampal volume, in which patients with depression have fewer dendritic spines. Abnormal functional neuroimaging (fMRI) studies of connectivity of brain circuits in depressed patients have also been reported (Grady and Stahl, 2015; Stahl, 2021).

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The Neuroprogression Hypothesis in Depression

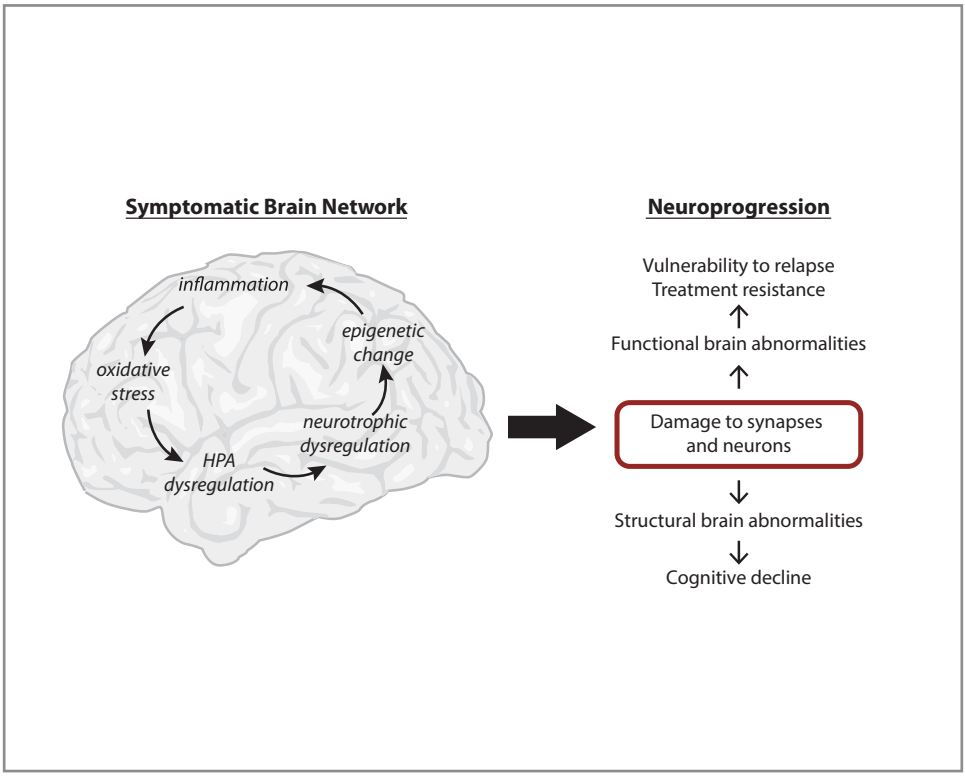

FIGURE 1.14. The neurobiological theory of neuroprogression is multifactorial. Neuroprogression in depression may be related to multiple interacting factors. Inflammation, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and oxidative stress may all influence neurotrophic dysregulation, resulting in epigenetic alterations that may further exacerbate inflammation, HPA axis dysfunction, and oxidative stress in a reciprocal fashion. Ultimately, all of these factors may contribute to the decrease in neurotrophic factors, the loss of synaptic connections, and the damage to neurons that may result in structural and functional brain abnormalities associated with depression (Stahl, 2021; Vavakova et al., 2015).

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The Hypothalamic-Pituitary-Adrenal (HPA) Axis

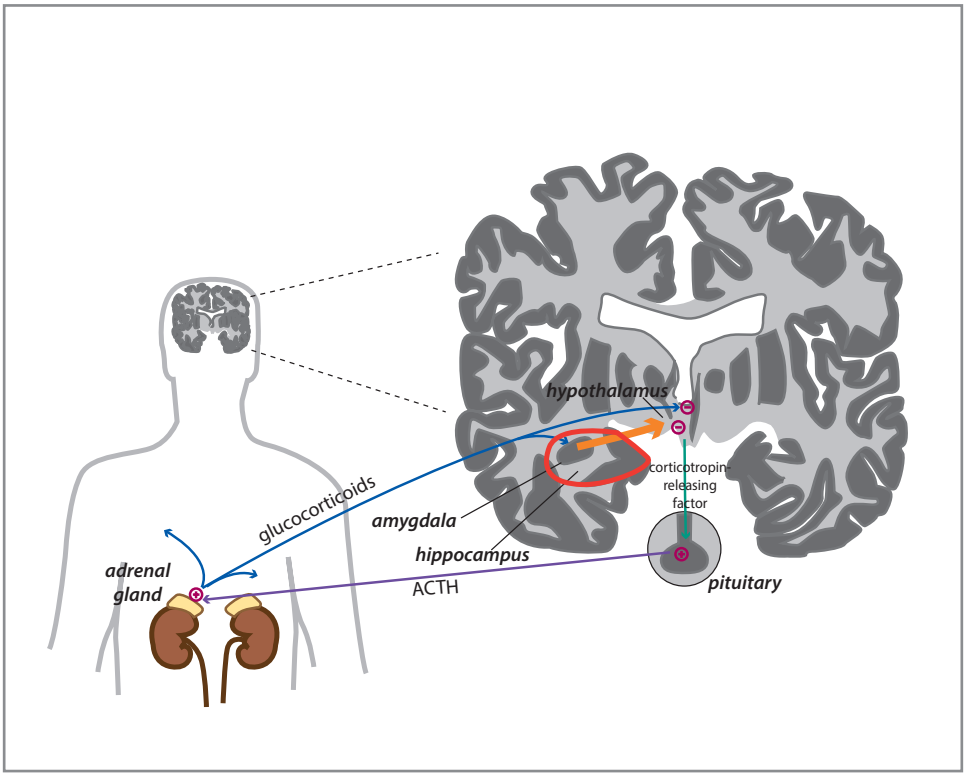

FIGURE 1.15. The normal stress response involves activation of the hypothalamus, resulting in increased corticotropin-releasing factor (CRF), which stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. The release of ACTH causes the adrenal glands to secrete glucocorticoids, resulting in negative feedback to the hypothalamus, and inhibits the release of CRF, terminating the stress response. The HPA axis is also suppressed via input from the amygdala and hippocampus (Keller et al., 2017; Stahl, 2021).

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Hippocampal Atrophy and Hyperactive HPA in Depression

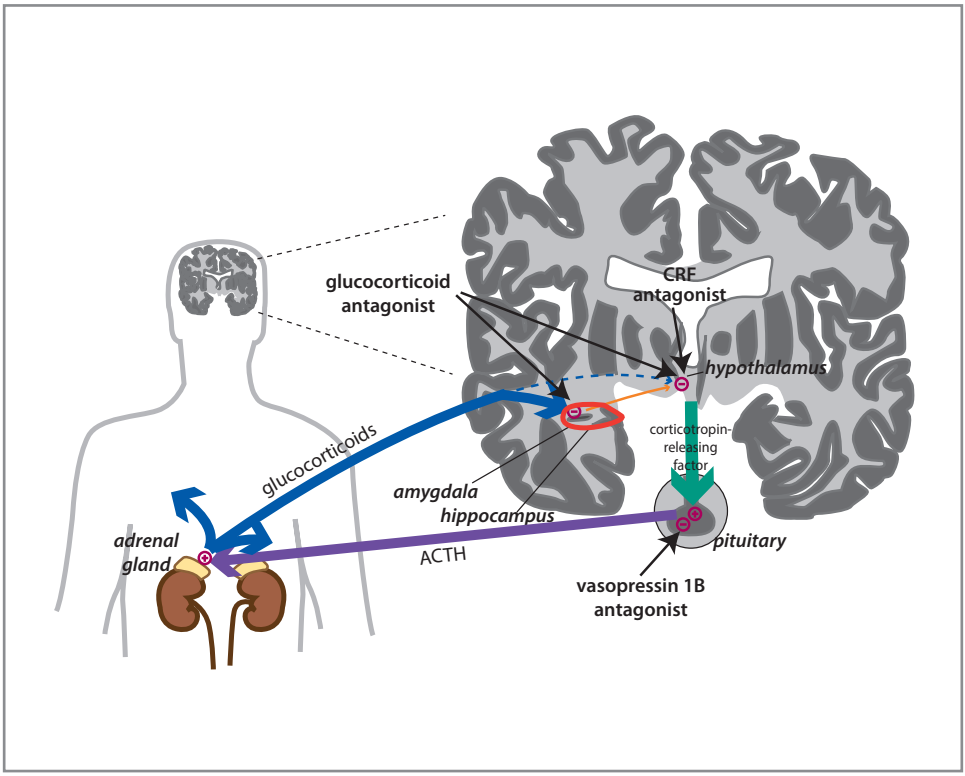

FIGURE 1.16. Neurons from the hippocampus and the amygdala normally suppress the HPA axis; thus, if chronic stress causes atrophy of hippocampal and amygdala neurons, the result could be overactivity of the HPA axis. Abnormalities of the HPA axis in depressed individuals have been reported, including reduction of negative feedback that inhibits the HPA axis, and elevated glucocorticoids. There is some evidence to suggest that high levels of glucocorticoids could be toxic to neurons. Novel antidepressant treatments that target CRF receptors and glucocorticoids are in testing (Keller et al., 2017; Stahl, 2021).

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Neuroinflammation in Depression

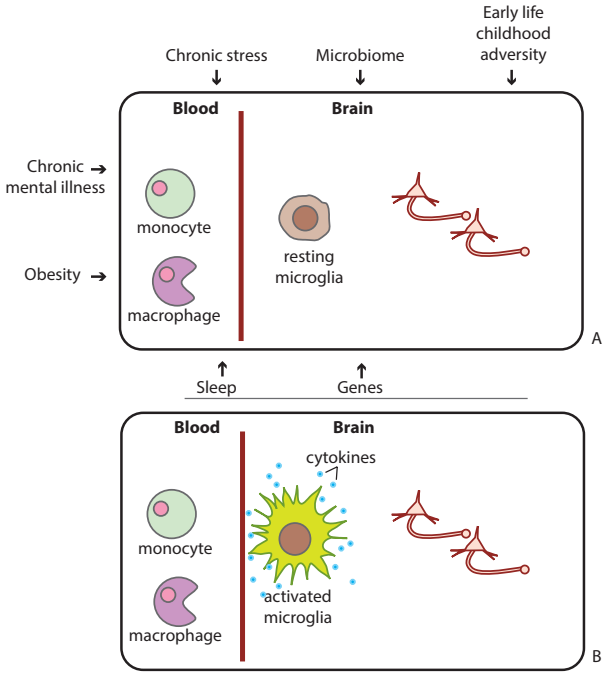

FIGURE 1.17. A) Chronic stress, early life adversity, obesity, chronic inflammatory diseases, long-term sleep disturbances, and disruption of the microbiome may all contribute to the development of neuroinflammation. B) When microglia become activated in the brain, due to these factors they can release proinflammatory cytokines (Brites and Fernandes, 2015; Stahl, 2021).

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Neuroinflammation in Depression: Microglia and Proinflammatory Cytokines

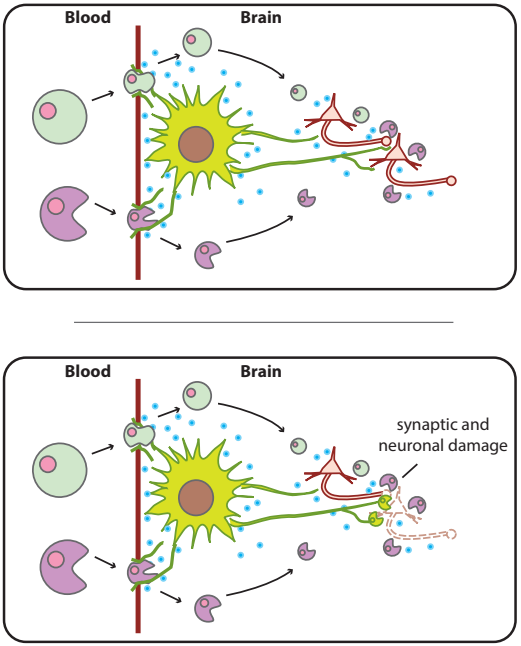

FIGURE 1.18. C) Proinflammatory cytokines attract immune cells, such as monocytes and macrophages, into the brain D) where they cause oxidative stress, HPA-dysfunction, reduction of growth factors like BDNF, and disruption of neurotransmission, and alter epigenetics to express unwanted genes that result in synaptic and neuronal damage (Brites and Fernandes, 2015; Stahl, 2021).

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Circadian Rhythm Hypothesis in Depression

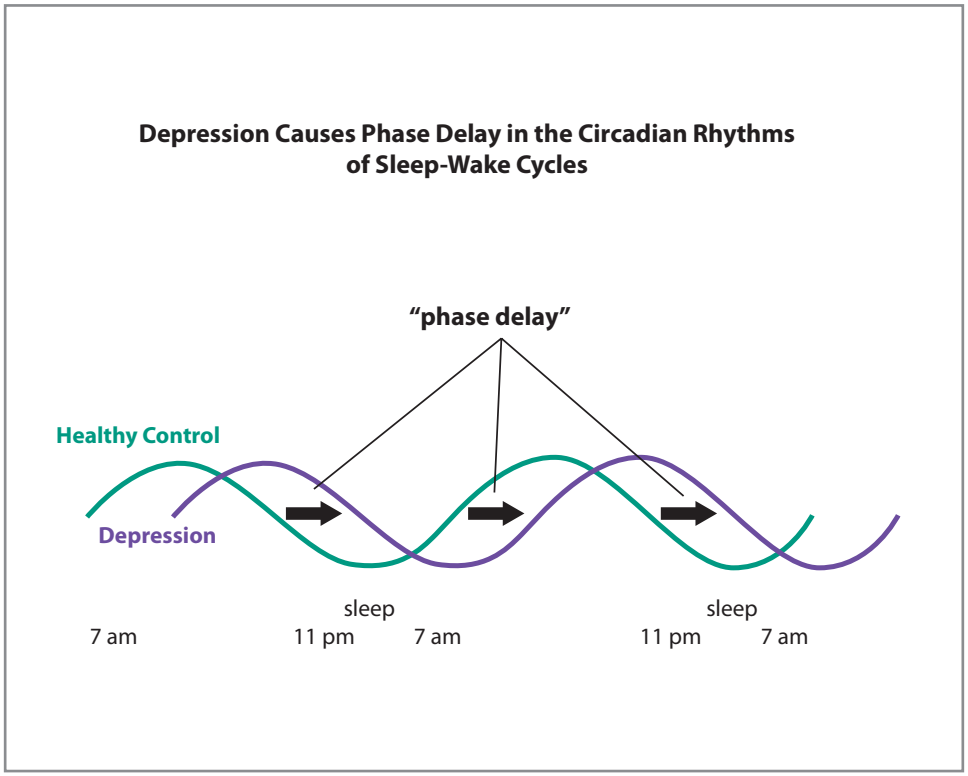

FIGURE 1.19. Another neurobiological model suggests that depression is a circadian rhythm disorder that causes a phase delay in the sleep/wakefulness cycle. In patients with depression, the circadian rhythm is often "phase delayed," meaning that wakefulness is not promoted in the morning, so patients fall asleep later. They also have difficulty falling asleep, so this results in daytime sleepiness. The extent of this phase delay is correlated with the severity of the depression. Desynchronization of biological processes, such as circadian rhythms, can be pervasive in depression. There are genes referred to as clock genes that are sensitive to light-dark and operate in a circadian manner. Abnormalities in various clock genes have been associated with mood disorders. For patients with a circadian rhythm disorder, treatments such as bright light therapy, melatonin, and sleep deprivation can have therapeutic effects (Satyanarayanan et al., 2018; Stahl, 2021).

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