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.

The Mood Disorder Spectrum

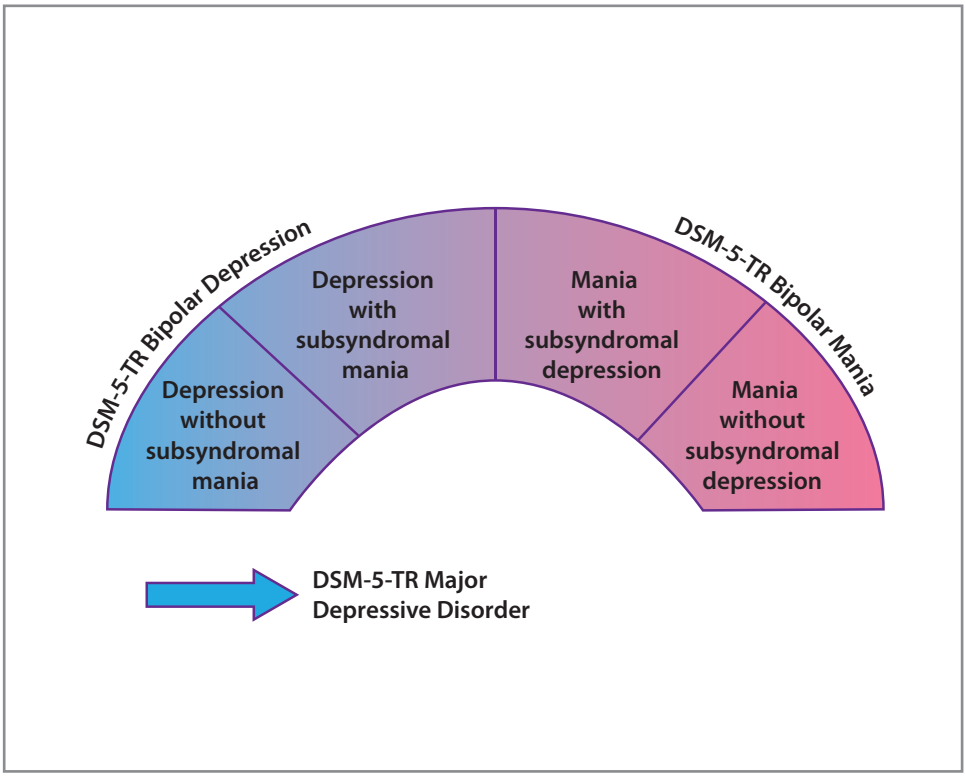

FIGURE 1.1. The field has moved away from characterizing depression and mania as distinct categories and now views them as opposite ends of a spectrum, with varying degrees of either or both between. Many patients are not purely manic or depressed, but rather they experience a mixture of symptoms. The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

Description of Depressive State Symptoms in Mood Disorders

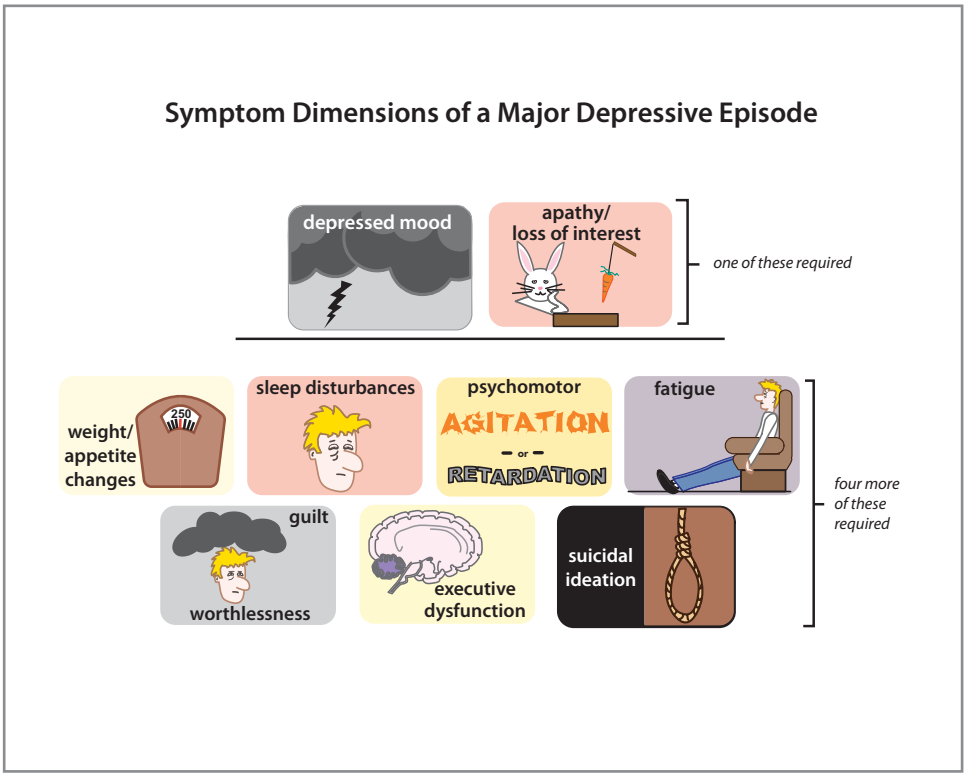

FIGURE 1.2. According to the DSM-5-TR (American Psychiatric Association, 2022), a major depressive episode is characterized by either depressed mood or loss of interest and at least four of the following: fatigue, insomnia/hypersomnia, weight/appetite alterations, fatigue, psychomotor agitation/retardation,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

Description of Manic State Symptoms in Mood Disorders

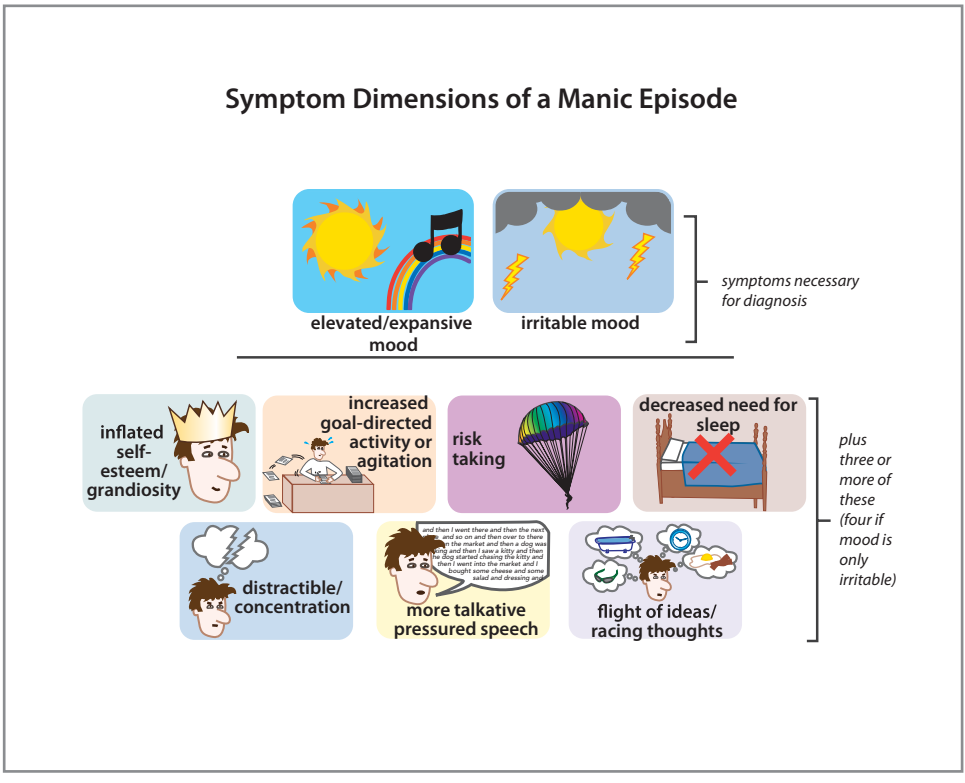

FIGURE 1.3. According to the DSM-5-TR, a manic episode consists of either expansive/elevated mood or irritable mood and at least three of the following (four if mood is irritable): increased goal-directed activity or agitation, inflated self-esteem/grandiosity, decreased need for sleep, risk taking,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

The Spectrum of Mood Disorder Symptoms

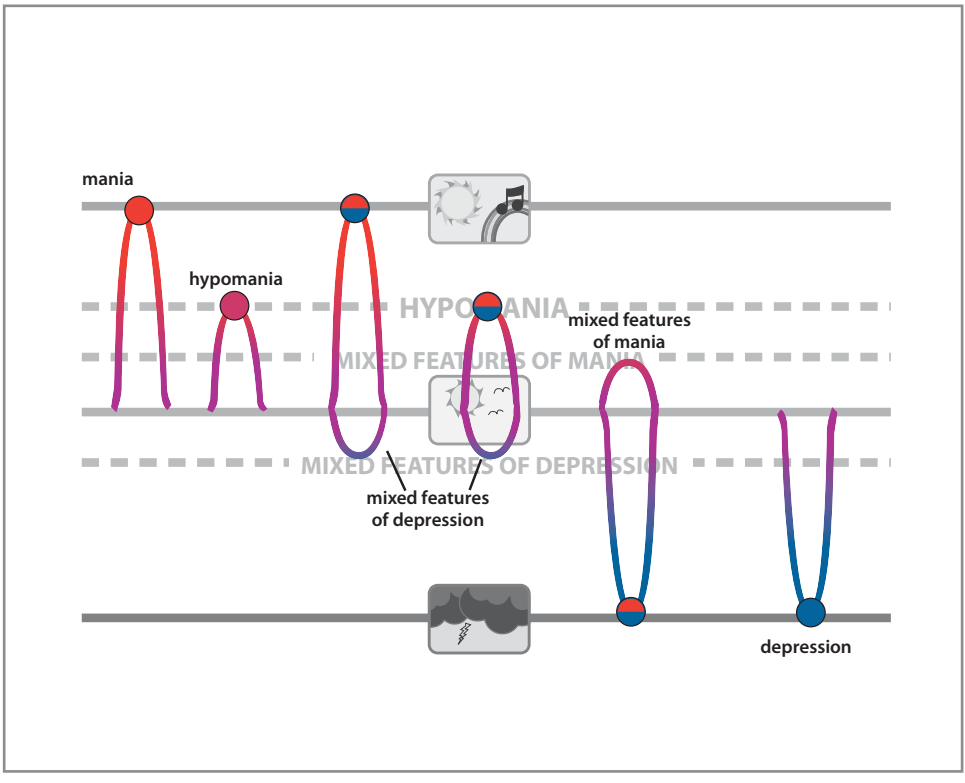

FIGURE 1.4. Mood disorder symptoms occur along a spectrum, with the polar ends consisting of pure mania or hypomania (the "up" pole) and pure depression (the "down" pole). Patients can also experience simultaneous symptoms of both poles. This is referred to as mania/hypomania with mixed features of depression, 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).

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).

Identifying Depression Within the Mood Disorder Spectrum

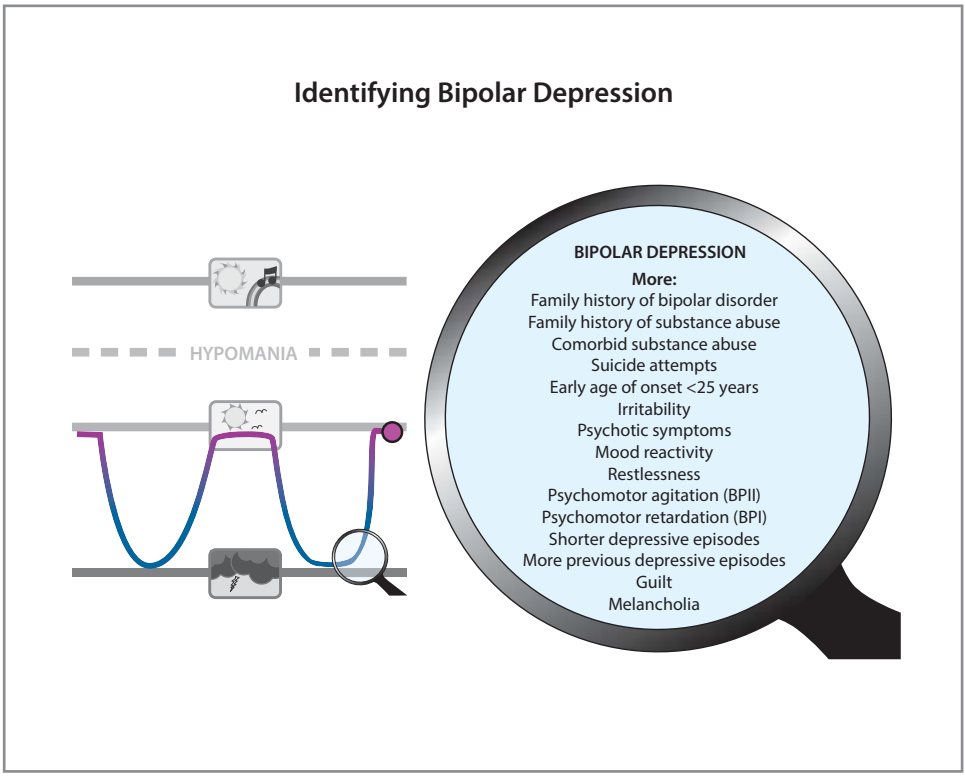

FIGURE 1.6. Aside from a history of prior manic/hypomanic episodes, patients with bipolar depression are diagnosed with identical criteria as patients with unipolar depression. While they may have similar symptoms, the long-term outcomes differ between patients with bipolar depression versus unipolar 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).

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.

Is Major Depressive Disorder Progressive?

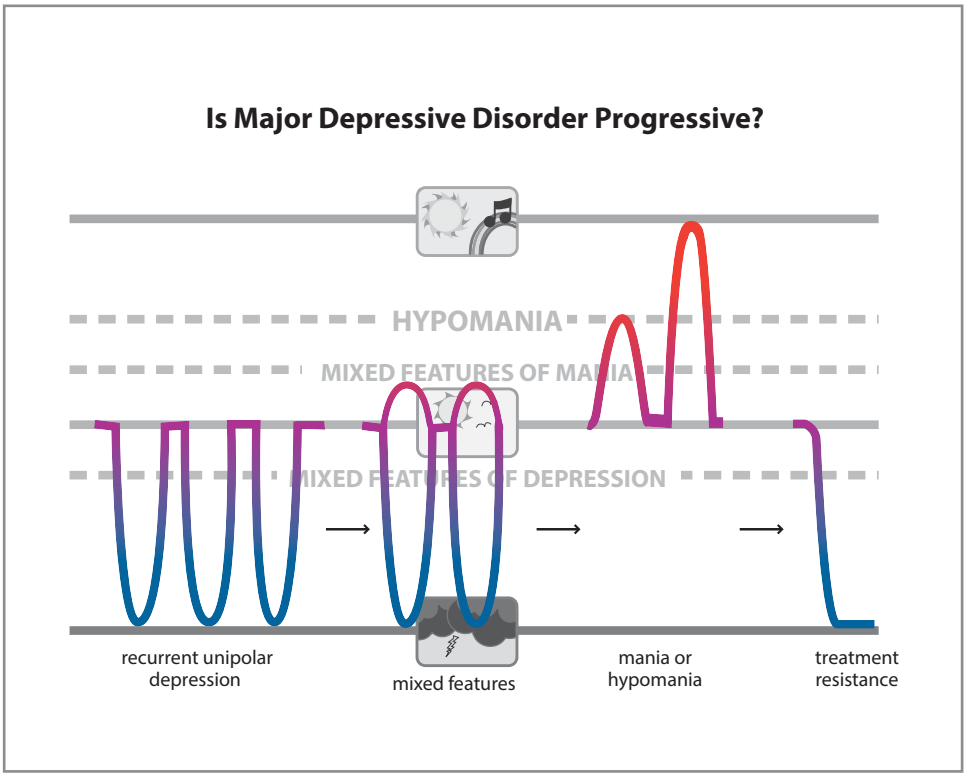

FIGURE 1.8. There is evidence that mood disorders may be progressive. While screening and monitoring patients with mood disorders it is essential to look for mixed features in depressed patients, whether they have unipolar or bipolar depression. There is evidence that unipolar depression can progress 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).

Evolving Disease Models in Depressive Disorders

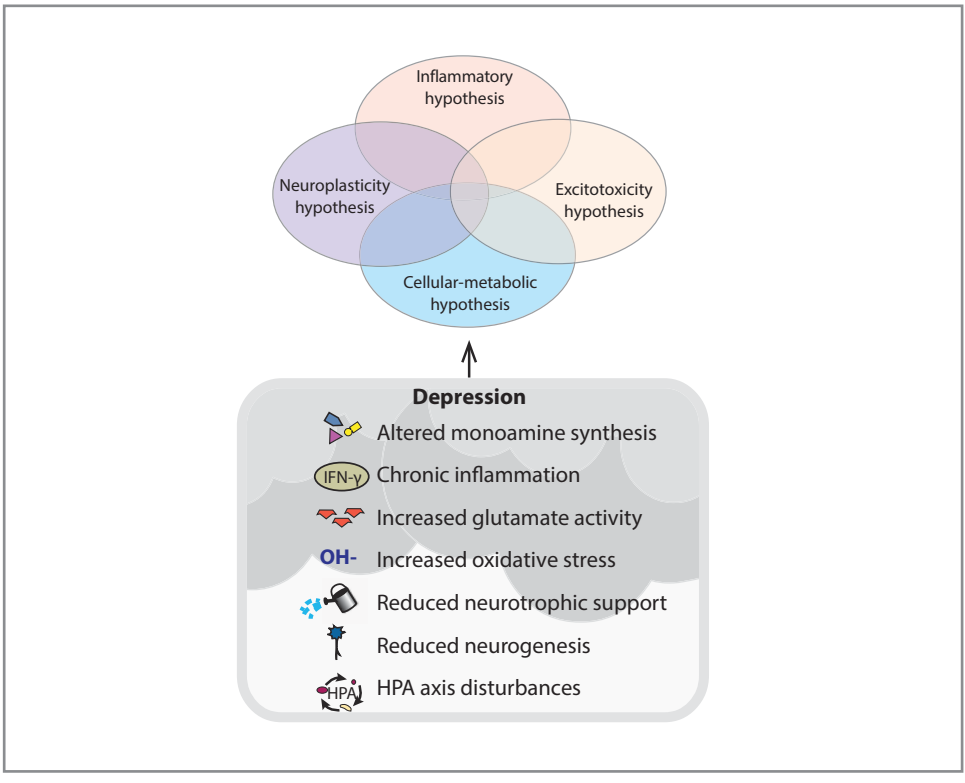

FIGURE 1.9. There is a growing body of research on the pathogenesis of depression identifying interactions between multiple biological systems. The major disease models are centered around altered monoamine functioning, chronic inflammation, excitotoxicity, neurogenesis and neuroplasticity disruptions/reduced 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.