

5 DEPRESSION

Let's begin our whirlwind tour of psychiatric pathology with **depression**. Depression has the highest lifetime prevalence of any single psychiatric disorder, with 20% of all people experiencing a depressive episode during their lifetime. Because of this, depression has been called the “common cold” of psychiatry. Despite how widespread it is, depression is not easy to diagnose. What we currently call “depression” is, in fact, an **illness with many faces**, and it is likely that the various disorders that we currently lump together under this term are in fact many separate conditions, each with their own unique causes and treatment considerations. It is this mix of **ubiquity** and **heterogeneity** that makes diagnosing depression such a challenge: most people have a preconceived idea of what “depression” means based on their own personal experiences, but this notion will differ drastically from one person to the next.



To help you make sense of this, we will first learn about depression in its most prototypical form: specifically, **episodic unipolar major depressive disorder** and its various subtypes. From there, we'll go over all the misdiagnoses and missed diagnoses that patients and medical professionals alike often lump together under the term depression. Because the approach to treatment can vary so widely for all the different clinical entities that are often called depression, it is imperative to accurately diagnose the situation as soon as possible. If you were to treat every person who walks through your door complaining of “depression” as if they have episodic unipolar major depressive disorder, you are likely to enter your patients into a cycle of failed treatments and dashed expectations. For this reason, knowing the patterns of “textbook” depression is essential.

SIGNS AND SYMPTOMS OF DEPRESSION

The specific signs and symptoms of depression are captured in the mnemonic **SIGECAPS**. Legend has it that SIGECAPS refers to an outdated practice where a doctor making a prescription would write “SIG” for directions and then “E-CAPS” for energy capsules, an older term for antidepressants. Use this memory device to remember:

S is for Sleep. Disturbances in sleep are a core symptom of depression and are experienced by more than 90% of people during an episode. Depression causes not only difficulty in falling asleep but also early morning awakenings, disrupting both the **amount** and **quality** of sleep that people are able to get. Research shows that depression is even able to alter someone’s circadian rhythm, making them feel perpetually jetlagged. Due to this, people with depression classically complain of severe symptoms of depression in the mornings which partially lift by the afternoon.

I is for Interest or enjoyment. A hallmark symptom of depression is an inability to feel pleasure, known as **anhedonia**. Anhedonia is evidenced by decreased interest in activities that are normally pleasurable such as participating in hobbies or socializing with others. Anhedonia is what makes depression a **non-reactive** state, meaning that someone’s mood will remain the same no matter what is going on around them. For example, someone in a state of depression would feel no joy even in situations that would normally inspire mirth, such as celebrating a birthday, getting a promotion at work, being with family and friends, or riding a giant chicken. Out of all the symptoms of depression, anhedonia is the **most sensitive** marker, and the absence of anhedonia reliably rules out major depressive disorder.



G is for Guilt or hopelessness. People in a state of depression often find that their thoughts become narrowed and, after a while, they are only able to focus on negative thoughts. The thought content in depression often revolves around feelings of **guilt** (“I deserve this”), **worthlessness** (“All I am is a burden on people”), or **hopelessness** (“There’s no way out of this hole I am in”). Thought patterns of depression are often **ruminative**, as certain thoughts are “chewed over” repeatedly in the mind.

E is for Energy. Levels of energy and activity are often severely decreased in depression, sometimes to the point where even getting out of bed in the morning is a major challenge. The **fatigue** seen in depression exceeds what would be expected just from the sleep disturbances present in this disorder, suggesting that fatigue is a core feature of the disorder rather than merely a side effect of other symptoms.

C is for Concentration. The rumination, poor sleep, and low energy experienced during a depressive episode often make it difficult to concentrate, leading to impairments in work, school, and relationships. In contrast to syndromes like attention deficit hyperactivity disorder where concentration deficits are chronic, in depression the ability to concentrate improves when the mood episode ends.

A is for Appetite. The majority of people with depression find that their appetite and food intake are significantly decreased, which can result in noticeable weight loss or even malnutrition over time. People in a state of depression often describe food as unappetizing or flavorless (“It’s like I’m eating cardboard”).

P is for Psychomotor retardation. While many features of depression are symptoms that can only be *subjectively* reported, in some cases depression involves signs that can be *objectively* observed by others. Psychomotor retardation refers to a general **slowing of speech and physical movements** which together suggest an inner slowing of cognition as well. It is generally considered to be a sign of severe depression.

S is for Suicidal thoughts. For people in the depths of depression who are unable to find any pleasure in life and are constantly haunted by feelings of guilt, worthlessness, and hopelessness, suicide can seem like the only way out. Over half of all people who die by suicide were in a depressive episode at the time of their death, making the link between depression and suicide incredibly robust.

A **major depressive episode** involves **depressed mood, anhedonia**, and a variety of **other signs and symptoms**.

Depressed mood + SIGECAPS:

Sleep disturbance

Interest or enjoyment (decreased)

Guilt or hopelessness

Energy (decreased)

Concentration (impaired)

Appetite (decreased)

Psychomotor retardation

Suicidal thoughts

Having **at least 5** of these 9 symptoms for **2 or more weeks** is diagnostic of a major depressive episode per DSM-5 criteria. However, it’s important to note that the DSM criteria do not capture the entirety of depression. There are a variety of additional signs and symptoms that are clinically seen in depression, including a slouched posture, monotone speech that lacks prosody, severe anxiety, a high rate of unexplained medical symptoms like headaches and stomach pain, feelings of depersonalization and derealization (“It’s like I’m seeing the world through a fog”), and a general lack of motivation. While not officially recognized in the diagnostic criteria, these signs and symptoms can be helpful for diagnosing depression as well.

Per the DSM-5, patients must have **5 out of 9** symptoms for a period of **2 weeks** or more to qualify for **major depressive episode**.

*The timeframe for depression is **two blue weeks**.*

DEPRESSION ACROSS THE LIFESPAN

The signs and symptoms of depression are important to understand, but ultimately they are only the first step in being able to diagnose depression. This is because evaluating signs and symptoms can only give you a cross-sectional snapshot of a patient at a single moment in time. However, diagnosis should be based on **longitudinal** information and take into account the patient's history across their entire lifespan as much as possible. Because of this, we will spend some time discussing the epidemiology, prognosis, and treatment response associated with depression to provide you with additional tools for getting the diagnosis right.



EPIDEMIOLOGY

As mentioned previously, depression is the single most common psychiatric disorder, with over 20% of all people experiencing at least one depressive episode during their lifetime. This gives depression a **high base rate** in the population, putting it high on your differential for *all* patients presenting with any psychiatric concern (even if you know nothing else about them). For patients specifically presenting with any kind of mood-related concerns, it should be at or near the top of your differential.

Depression can develop at any age, although it begins most often in **early adulthood** with a median age of 32. However, up to a quarter of people with depression do not have their first episode until after the age of 50, so a lack of prior episodes (even in an elderly patient) does not automatically rule out a major depressive episode. **Women** are diagnosed with depression twice as often as men.

PROGNOSIS

Evaluated longitudinally, the signs and symptoms of major depressive disorder tend to occur in discrete **episodes**. Untreated, an episode of depression usually lasts between **6 to 12 months**. After this time, most patients will spontaneously recover and enter a period of normal reactive mood known as **euthymia** (although many will have some residual depressive symptoms even between episodes). Functioning is often significantly impaired *during* an episode of depression but **preserved between episodes**. (This is in contrast to other disorders, such as schizophrenia or personality disorders, where functioning is continuously impaired.)

After a single episode of depression, the risk for developing another episode is approximately 50%. This means that as many as half of all people diagnosed with depression will only have a single **isolated** episode during their lifetime. For the other half, depression becomes a **recurrent** disorder, with the risk of recurrence increasing to 80% after a second lifetime episode and getting even higher with each additional episode after that.

The relationship between depression and life events is complex. Although exact numbers are hard to come by, depressive episodes are *sometimes but not always* precipitated by stressful life events. Generally, these life events involve some form of a major disruption to one's **social circumstances**, with the most common being conflict with one's partner, moving geographically, being forced to change jobs, receiving a diagnosis of a major medical illness, having a family member leave home, or

experiencing the death of a relative or close friend. Interestingly, the relationship between major life events is most clearly established for one's first lifetime episode of depression. After that, depression seems to take on "a life of its own," with episodes happening more and more often without a clear link to life events.

Depression carries a significant **mortality rate**. Mood disorders are found in the majority of people who die by suicide, and up to 5% of people with depression will eventually take their own lives. Depression also worsens outcomes for a variety of medical illnesses including cancer, heart disease, and stroke, leading to decreases in life expectancy of up to 10 years even after removing suicide from the equation.

TREATMENT

With treatment, the average length of a major depressive episode is reduced from 6 months to less than **3 months**. Treatment for depression consists of **psychotherapy**, **medications**, or a **combination** of the two. While psychotherapy and antidepressants are both effective, the combination of the two is better than either one alone.

Several types of psychotherapy have been shown to be helpful. The most well-studied is **cognitive behavioral therapy** (CBT) which focuses on the connections between thoughts, feelings, and behavior and teaches specific skills for breaking out of the cycle of depression. CBT is associated with a **medium effect size** (around 0.5) for treating depression. Other types of therapy, including behavioral activation, acceptance and commitment therapy (ACT), interpersonal therapy (IPT), and psychoanalytic therapy, have evidence supporting their use as well.

Medications used to treat depression are known as **antidepressants**, although this is a marketing term more than a scientific one. Most of these drugs work by increasing the amount of various neurotransmitters, including **serotonin**, **dopamine**, and **norepinephrine**, that is active and available in the brain. The most common class of antidepressant is **serotonin reuptake inhibitors** (SRIs) that boost levels of serotonin in the brain, although other neurotransmitters like norepinephrine and dopamine can play a role as well. Antidepressants are helpful for treating depression, with a **small-to-moderate effect size** of around 0.4. Antidepressants also take some time to work, with a full effect often not being seen for up to 2 months after beginning the medication.

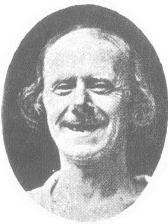
Treatment response in depression appears to follow a "Rule of Thirds," as about one-third of patients who receive treatment experience complete recovery from their symptoms (known as **remission**), one-third notice the improvement of some but not all symptoms (known as **response**), and one-third do not get any better with the first treatment tried (known as **treatment resistance**). Patients who have not received any benefit even after multiple trials of therapy and medications are considered to have **treatment-resistant depression**. In these cases, treatments such as electroconvulsive therapy (ECT) may be considered. While ECT is an invasive and complicated procedure, it is highly effective, with a **large effect size** around 0.8 even for people who have not received any benefit from other treatments tried.

MECHANISMS OF DEPRESSION

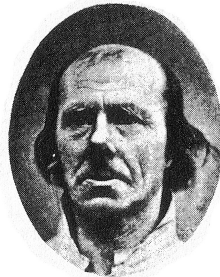
Throughout this book, we will explore what is known about the underlying pathophysiology of the disorders that we are studying with the goal of using this information both to improve diagnostic accuracy as well as to identify those people who are most likely to benefit from specific treatments. However, it is worth keeping in mind that the brain is a complicated organ, and given how little we know about it, these mechanisms should be seen as **likely hypotheses** rather than established facts.

Looking at the pathophysiology of this condition, it is worth stating right off the bat that there is **no evidence that depression results from an inherent “chemical imbalance”** of any kind. While medications that increase serotonin are effective at reducing the symptoms of depression in the majority of people who take them, that does *not* mean that depressed people lack serotonin, and decades of research have yet to provide much evidence for the “chemical imbalance theory” of depression.

Instead, depression appears to involve specific changes in the way that people process information. To put it simply, depressed people see the world differently. Depression involves a tendency to focus on negative, rather than positive, stimuli. When presented with a list of words, for example, people with depression are more likely to focus on words like “hate” or “pain” rather than “love” or “comfort.” When shown a variety of faces, a depressed person will fixate on people with negative facial expressions (like anger or disgust) while blocking out those with positive expressions (like smiling or laughter). Like an invisible magnet, depression draws one’s mind preferentially towards negative stimuli, not only in terms of what occupies attention in the current moment but also what information is remembered weeks or months down the line.



*Perspective of a **non-depressed** person.*



*Perspective of a **depressed** person.*

On a neurobiological level, these differences in emotional processing are reflected in the amygdala and other parts of the **limbic system**. In someone who is depressed, these brain regions are *hyperactive* when shown a sad or angry face and *hypoactive* when shown happy or smiling faces. This phenomenon is referred to as a **negative affective bias**: *negative* for sad or pessimistic, *affective* for one’s current emotional state, and *bias* for being drawn to certain stimuli over others. Negative affective biases tend to accumulate, trapping people in a vicious cycle where the negative thought patterns of depression are constantly reinforced.

Negative affective biases explain much of what is seen in the phenomenology of depression. For one, each person at their baseline has an intrinsic tendency to focus on either positive or negative stimuli and, like many things in psychiatry, this occurs

on a spectrum. Research has found that people who have a greater tendency towards negative emotional processing (even when not in an episode of depression) are at higher risk for developing depression compared to people with a greater tendency towards positive stimuli, suggesting that this represents an **inherent vulnerability** towards depression regardless of one's current mood state. In addition, negative affective biases tend to accumulate in a **snowball-like effect**, explaining the “slide” into depression that people experience (rather than depression being a state that comes on all at once like a flu). Finally, negative affective biases lead people with depression to consistently **underestimate their chances of success** at various activities, leading to the specific cognitive and behavioral patterns seen in depression such as feelings of hopelessness (“I never do anything right”), isolating oneself socially (“I’m not going to see people, they will all just laugh at me”), and a lack of desire to engage in pleasurable or rewarding activities (“Maybe it works for other people, but it won’t work for me”). (This tendency towards *underestimation* of success will form the basis of a crucial distinction between depression and mania in the next chapter.)

The involvement of negative affective biases also explains much of what we see during treatment of depression. In particular, negative affective biases provides a mechanism for why antidepressants take so long to work. As mentioned previously, antidepressants often take up to 2 months to have a full effect, which makes them different from other drugs (like stimulants or alcohol) that exert psychological effects almost immediately after taking them. However, studies have demonstrated that antidepressants *do* in fact have immediate effects—just not the ones you might expect. Within minutes of taking an antidepressant, a significant lessening of negative affective biases is observed, with people becoming more able to focus on positive stimuli, less reactive to negative facial expressions, and more accurate at estimating their chances of success at various activities. It is believed that this change in emotional processing sets the stage for a *gradual* unlearning of depressive thought patterns and behaviors. In fact, studies have found that the extent to which an antidepressant will ultimately improve mood for a particular person can be predicted by how much it changes their affective processing within the first few days of treatment. Negative affective biases also explain why antidepressants do not elevate mood in non-depressed people (they are not “happy pills”), as they won’t work if there are no negative affective biases to lift. They also explain why drugs and CBT are both effective in treating depression and in roughly the same amount of time, as both types of treatments reduce negative affective biases and allow someone with depression to establish new thoughts patterns and different ways of interpreting the world.

No one theory is going to explain a condition as complex as depression, and additional mechanisms are likely at work (including prominent dysregulation of the **hypothalamic–pituitary–adrenal axis**, discussed further in Chapter 9). Nevertheless, negative affective biases serve a practical purpose by helping to confirm a diagnosis of depression and to provide a specific neurobiological target for treatment.

HOW TO DIAGNOSE DEPRESSIVE DISORDERS

Like most mental disorders, a diagnosis of depression is determined primarily using the psychiatric interview and the mental status exam. Specific symptoms of depression, as well as their timing across the lifespan, should be directly assessed. Certain findings on the mental status exam (including slowed movements, absent prosody, dysthymic affect, a ruminative thought process, and suicidal ideation) may also argue for the diagnosis.

Even once you have diagnosed major depressive disorder, however, your job is not yet done. There are various **subtypes** of major depressive disorder that should be considered as well, all of which fit the phenomenology and life course of “textbook” depression to some extent. The presence of any of these subtypes can carry implications for treatment, so make sure to keep them on your differential. Unlike the misdiagnoses and missed diagnoses we will talk about in the next section, all of these entities would accurately be considered to be unipolar major depressive disorder.

MAJOR DEPRESSIVE DISORDER

Major depressive disorder is the prototypical depressive disorder and can be diagnosed when the SIGECAPS symptoms are present for at least two blue weeks. Notably, these episodes of depression occur *without* accompanying episodes of mania (making it a *unipolar*, rather than a *bipolar*, disorder). Even a *single* major depressive episode is sufficient to diagnose major depressive disorder per DSM-5 standards despite the fact that only 50% of people will go on to have another episode. For clarity, people with multiple episodes of depression are said to have **recurrent** major depressive disorder.

MELANCHOLIC DEPRESSION

Historically, the “melancholic” specifier was used to describe **severe** episodes of depression that seemed to come “out of the blue” (as opposed to being brought on by life events) and were completely **non-reactive** to external circumstances. **Neurovegetative symptoms** such as psychomotor retardation, severe loss of appetite, weight loss, fatigue, inattention, and disrupted sleep are particularly pronounced. It is unclear if melancholic depression represents a distinct subtype of major depressive disorder as opposed to simply a very severe form. In any case, treatment is largely the same as for “textbook” depression, although more intensive forms of treatment such as ECT may be considered earlier.

ATYPICAL DEPRESSION

Atypical depression has some unique features compared to “textbook” depression. Most notably, mood remains **reactive** in atypical depression, and many people with atypical depression will experience a lifting of depressive symptoms during happy life events or a worsening of symptoms when things don’t go their way. Patients with atypical depression often display a long-standing pattern of **interpersonal rejection sensitivity**, even when not in an episode of depression. Other unique features of atypical depression are an *increase* in appetite (rather than a decrease) which can result in weight gain, sleeping too much (rather than too little), and a



sensation that one's limbs feel too heavy to lift (known as **lead**en paralysis). In terms of treatment, a specific class of antidepressants known as **monoamine oxidase inhibitors** (MAOIs) is particularly effective for atypical depression. You can remember the features of atypical depression by thinking of it as **ate-typical depression**: a depressed person who had mood reactivity and became happy when they **ate** food would probably start to gain weight, causing their limbs to feel heavy, and may become sensitive to people rejecting them because of their weight.

Atypical depression involves **increased appetite, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity.**

*Ate-typical depression involves **eating**, leading to **heaviness** and **rejection sensitivity**.*

POSTPARTUM DEPRESSION

Around 15% women develop clinical depression within a few weeks of delivering their child. It is unclear why the postnatal state increases the risk of depression, but many factors (including hormonal changes, sleep deprivation, and childcare stress) are believed to play a role. Postpartum depression is not considered to be a separate syndrome from major depressive disorder and is treated like “textbook” depression with the exception of taking some additional considerations into account when choosing medications if the mother is breastfeeding.

Postpartum depression should be differentiated from “**baby blues**,” a transient state of mild depressive symptoms that resolves within a few weeks. Baby blues occur in 80% of mothers following delivery and are considered to be a normal part of the human experience. Severe symptoms lasting more than a few weeks should raise the consideration for a diagnosis of postpartum depression (remember “two blue weeks”). Postpartum depression should also be carefully separated from **postpartum psychosis**, another psychiatric syndrome that occurs in the period following childbirth. In contrast to baby blues or postpartum depression, postpartum psychosis is characterized by symptoms of psychosis or mania, including rapid swings in mood, hallucinations, bizarre beliefs, and paranoia. Postpartum psychosis is one of the leading causes of infanticide and is considered to be a medical emergency necessitating immediate psychiatric hospitalization and treatment.



PSYCHOTIC DEPRESSION

Psychotic depression is characterized by the presence of **paranoia, delusions, or hallucinations** in addition to all of the usual symptoms of major depressive disorder. Psychotic symptoms do not occur in all cases of severe depression, but nearly all cases of psychotic depression involve severe depressive symptoms. Treatment involves a combination of both **antidepressants** and **antipsychotics**. In many cases, hospitalization and/or ECT should be considered. (Differentiating psychotic depression from other disorders where mood and psychotic symptoms co-occur, including bipolar disorder with psychotic features, schizoaffective disorder, and even

schizophrenia itself, can be challenging. We will defer discussion of this until Chapter 7, as it requires a greater understanding of both mania and psychosis.)

CATATONIC DEPRESSION

Catatonia can occur in severe cases of major depressive disorder. It manifests in the specific signs and symptoms described in Chapter 4 and often requires intensive treatment in a hospital setting. As with all forms of catatonia, **benzodiazepines** should be used liberally, as they are often very effective at rapidly reversing the state of catatonia. If medications are not effective or if there are signs suggestive of malignant catatonia, ECT should be considered.

SEASONAL DEPRESSION

Seasonal depression (also known as seasonal affective disorder) is a subtype of major depressive disorder where depressive episodes have a clearly established link with the changing of the seasons. Most often, depression develops during the **winter months**. This is likely related to lower levels of sunlight during the winter, as the rate of seasonal depression increases the farther away from the equator you go.



Treatment for seasonal depression involves **bright light therapy** for at least 30 minutes each day to help offset the loss of sunlight. Most houselights do not produce the full spectrum of light (as sunlight does), so specialized “light boxes” should be used. Standard treatments for major depressive disorder, including conventional antidepressants and psychotherapy, can be used as well and are equally effective.

DIFFERENTIAL DIAGNOSIS OF DEPRESSIVE DISORDERS

Now that we have a good understanding of depression and its various subtypes, let’s explore what actually happens when patients walk into the door complaining of “depression.” Even the most well-read students can have difficulty adjusting to real-world clinical settings where cases of “textbook” depression are the **exception rather than the rule**. Even in cases where someone *technically* meets diagnostic criteria for major depressive disorder, a different diagnosis (such as bipolar disorder or borderline personality disorder) may do a much better job of explaining the patient’s distress and pointing towards a helpful treatment strategy. This reflects a major shortcoming of the DSM and other algorithmic approaches to diagnosis: they have increased the *reliability* of diagnosis at the expense of sacrificing the *validity* of what the diagnostic criteria are supposed to represent.

For this reason, when evaluating a patient complaining of depression, it can be helpful to approach the psychiatric evaluation with an eye towards **misdiagnoses** and **missed diagnoses**. Misdiagnoses are fundamentally incorrect diagnoses. For example, if someone with a history of both depression and mania was diagnosed with unipolar (rather than bipolar) depression, this would simply be a wrong diagnosis. In contrast,

missed diagnoses are those that are frequently encountered with depression (such as anxiety or substance abuse) and can interact with or mimic many of its symptoms. Understanding the most common misdiagnoses and missed diagnoses of depression can be exceptionally challenging, even for experienced clinicians. It will be even more challenging early in this book, as we will not have discussed many of the conditions we will be comparing with depression. Rest assured that it will get easier as you progress in knowledge. In the meantime, feel free to jump ahead to other chapters of the book to gain additional insight into these disorders.

Both when answering test questions as well as when evaluating patients in clinical settings, having a framework for evaluating mood concerns can give you a structured process for picking up on clinically important features. You can use the mnemonic **Reactive PLANETS** to remember the specific high-yield factors that commonly differentiate depression from alternative diagnoses:

R is for Reactivity. The presence or absence of mood reactivity is an important diagnostic clue. Non-reactivity suggests a mood disorder such as unipolar or bipolar depression, while a reactive mood may suggest atypical depression, borderline personality disorder, or even just plain old normalcy.

P is for Polarity. A history of both depression and mania is the diagnostic hallmark of bipolar disorder. Make sure to inquire about any history of manic or hypomanic episodes, as bipolar depression requires a fundamentally different treatment approach compared to unipolar depression.

L is for Lability. Mood symptoms can either be stable or labile. Mood symptoms from major depressive disorder or bipolar disorder are often quite stable and endure for weeks, months, or years at a time. In contrast, a labile affect (changing within minutes or hours) is often more characteristic of personality disorders or substance use.

A is for Attributability. In some cases, depression can be attributable to specific causative factors, including medical conditions (like hypothyroidism), substances (alcohol), external circumstances (postpartum depression), and timing (seasonal depression or premenstrual dysphoric disorder) among many others.

N is for Normality. Normalcy should *always* be on the differential. Take some time to consider whether the patient's reported symptoms are within the realm of normal human emotion.

E is for Episodicity. Depressive symptoms often occur in discrete episodes, which is characteristic of both unipolar major depressive disorder as well as bipolar disorder. Chronic non-episodic depression should raise your suspicion for other diagnoses, including dysthymia and personality disorders.

T is for Treatment responsiveness. How well a person has responded to treatments for depression can offer a helpful clue as well. A history of failing multiple trials of conventional antidepressants should have you searching for alternate explanations, including misdiagnoses (bipolar disorder), missed diagnoses (anxiety disorders), or

other attributable factors (alcohol-induced depression). However, poor treatment response in and of itself is not sufficient to rule out major depressive disorder (they may just have treatment-resistant depression). The best way of conceptualizing the effect of treatment response is to think that poor treatment response *can be but is not always* a marker of a misdiagnosis or missed diagnosis.

S is for Severity. Finally, the severity of depressive symptoms can help to differentiate between “full blown” and subsyndromal symptoms of depression as well as to differentiate between normalcy and pathology.

Diagnosing depression is more than just using **SIGECAPS**! Try to focus on the patient’s pattern of symptoms **across the lifespan**.

Use **Reactive PLANETS** to systematically assess mood complaints:

Reactivity

Polarity

Lability

Attributability

Normality

Episodicity

Treatment responsiveness

Severity



NORMALCY

Sadness, grief, misery, distress, and heartache are painful, and it’s not uncommon for people to seek psychiatric care when they experience these emotions. However, to label these experiences as a mental disorder risks unnecessarily pathologizing normal human emotion. When deciding where to draw the line between illness and pathology, consider both **reactivity** and **severity**. For example, someone who recently lost a spouse after a long battle with cancer is likely to experience grief. The symptoms of grief overlap significantly with those of depression, including an intense and protracted state of poor mood, difficulty enjoying activities, trouble

concentrating, poor appetite, and difficulty sleeping. However, most people agree that grief should ultimately be considered a normal part of the human experience and not be diagnosed as a mental disorder. Focusing on reactivity and severity can help to identify those cases where distress and dysfunction are clearly in excess of what most people would experience during grief. While many people experience intense sadness while grieving, it is a minority of people who have a completely non-reactive mood, who are unable to focus on any positive stimuli, who feel completely hopeless about the future, who begin to feel worthless or lack self-esteem, or who begin having persistent thoughts of suicide following bereavement. In these cases, the line between normalcy and pathology has been crossed, and a discussion of treatment options may be helpful. While bereavement is only one example, it provides a good case study for demonstrating the challenges of separating normalcy from depression.

It's also not uncommon for people to use the language of depression as an **idiom of distress**. For example, someone who is upset because they did not get a promotion at work may tell others "I'm depressed" as a way of communicating and seeking validation for their emotions. Distress is not inherently pathological, so always make sure to ask further questions before giving a clinical diagnosis.

ADJUSTMENT DISORDER

Adjustment disorder is defined as depressive and/or anxious symptoms that occur soon after a major life stressor such as going through a divorce or losing a job. Given that we have already established that depressive episodes can also occur after major life events, how can we differentiate between depressive episodes and adjustment disorder? The key here is that the symptoms are **not so severe** that the patient would meet criteria for clinical depression. In effect, adjustment disorder is a "**diagnosis of normalcy**" that recognizes that some degree of distress is normal and expected following a major life change. The continued existence of adjustment disorder as a diagnosable "mental disorder" likely reflects the fact that it ultimately serves a practical purpose by allowing clinicians to provide treatment for grieving or suffering patients in a way that is normalizing, non-stigmatizing, and permits reimbursement for medical services. Treatment for adjustment disorder involves a specific type of psychotherapy known as **supportive therapy** that allows the patient to discuss their psychological reactions in a setting that is empathic and compassionate.



DYSTHYMIA

Dysthymia (referred to as "persistent depressive disorder" in the DSM-5) is on the spectrum of depression but differs from major depressive disorder in two crucial ways. First, it is **chronic** rather than episodic, with symptoms being present most of the time without a break for **at least two years**. Second, it is **subsyndromal** in that the patient does not quite meet full criteria for a major depressive episode but still suffers from depressed mood. Mood symptoms in dysthymia tend to avoid those symptoms of depression that are generally found more often in severe cases of depression (such as psychomotor retardation or thoughts of suicide). This suggests that dysthymia can be

conceptualized as a milder but more chronic form of major depressive disorder, and this idea is supported by the fact that treatment for dysthymia is largely the same as for “textbook” depression. You can remember the common symptoms and time course of dysthymia using the mnemonic **HE’S 2 SAD** to remind you of the **H**opelessness, decreased **E**nergy, low **S**elf-esteem, abnormal **S**leep, **A**ppetite changes, and impaired **D**ecision-making that are seen, all for a minimum of **2** years.

Dysthymia (also known as persistent depressive disorder) is a state of **chronic depressive symptoms** that are less severe than “textbook” depression.

HE’S 2 SAD:

Hopelessness

Energy (decreased)

Self-esteem (decreased)

2 years minimum

Sleep (abnormal)

Appetite (abnormal)

Decision-making (impaired)

Up to a quarter of all patients with depression have both dysthymia and major depressive disorder, a clinical situation known as “**double depression**.” In these cases, the patient spends large portions of their life in a chronic subsyndromal state of depression punctuated with discrete episodes of more severe depression. People with double depression also tend to relapse much more quickly than those with “textbook” major depressive disorder. Double depression is notoriously difficult to treat, but the approach to treatment remains the same: therapy and/or medications.

BIPOLAR DEPRESSION

Depression that occurs in someone with a history of mania or hypomania should be diagnosed as bipolar (rather than unipolar) depression. Clinically, bipolar depression is often **indistinguishable from unipolar depression**. However, major differences in prognosis and treatment response between unipolar and bipolar depression suggest that these two conditions should be conceptualized as **entirely separate disorders** despite the significant overlap in symptoms. A patient presenting with current depressive symptoms can be diagnosed with bipolar I disorder if there is a clear history of even a single manic episode, while a history of even a single hypomanic episode is sufficient to diagnose bipolar II disorder. (Both mania and hypomania will be discussed further in Chapter 6.)

What complicates the process significantly is the fact that patients who have bipolar disorder will often have several depressive episodes *before* their first manic episode. How can we be certain that a patient having their first major depressive episode is not, in fact, presenting with bipolar depression? After all, around 15% of all people seeking treatment for depression will ultimately be diagnosed as having bipolar disorder, and 40 to 70% of people with bipolar disorder are initially diagnosed with unipolar depression. There are some clues that can point us in the right direction. Compared to people with unipolar depression, people with bipolar depression tend to

have their first episode earlier in life, to spend more of their time impaired by mood symptoms, to have more psychomotor retardation, to display melancholic, atypical, or psychotic features, and to have a family history of mania. Treatment response can be helpful as well, as conventional antidepressants are likely to be ineffective and may actually increase the rate at which the patient alternates between mania and depression (known as “rapid cycling”). Pay close attention to the presence of any of these during the initial evaluation as well as subsequent treatment. However, at the end of the day, none of these clues are sufficient to definitively diagnose bipolar depression, and **you can never be certain** that a patient has bipolar disorder until they have “declared themselves” by having their first manic or hypomanic episode. While operating within this kind of ambiguity can be frustrating, it is worthwhile to be cautious before diagnosing bipolar depression, especially considering that the treatments for bipolar disorder (including mood stabilizers and antipsychotics) are significantly more harmful than those for unipolar depression.

CYCLOTHYMIA

Just as dysthymia can be conceptualized as a milder but more chronic form of depression, so too cyclothymia can be seen as a milder but more chronic form of bipolar disorder. Cyclothymia can be differentiated from unipolar depression by its **lower severity** and **bipolarity**. In cyclothymia, someone has periods of mild depression (that never quite meet criteria for a major depressive episode) alternating with episodes of hypomania (that never quite meet criteria for a manic episode). While conceptually cyclothymia makes sense, in practice it is rarely diagnosed as most people who have either manic or hypomanic episodes tend to have “full blown” major depressive episodes at some point during their lives.

SUBSTANCE INDUCED MOOD DISORDER

The relationship between depression and substance use is often a two-way street. The effects of certain drugs (such as alcohol or benzodiazepines) can resemble depression during intoxication, while others (including stimulants like methamphetamine) can resemble depression during withdrawal. Other substances may induce depression to the extent that someone may be depressed even when they are not actively intoxicated. The most common substance associated with depression is **alcohol**, but even prescription drugs (such as benzodiazepines or steroids) can impact mood. The key for diagnosing a substance-induced mood disorder is **attributability** and **timing**, as use of the substance will often correlate with increases in depressive symptoms while abstaining from the substance will tend to resolve the symptoms. In cases where symptoms persist even after substance use is stopped for some period of time, a diagnosis of a primary depressive disorder should be considered.

MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION

Certain medical conditions can “masquerade” as depression and remain undiagnosed for long periods of time. A classic example is **hypothyroidism**, a condition whose symptoms (such as fatigue and poor appetite) overlap significantly with and are often mistaken for clinical depression. Other examples include cardiac disease, chronic hypotension, infections, certain forms of cancer, and neurologic disorders such as multiple sclerosis. The key is for the clinician to have a **high index of suspicion** for any

physical signs or symptoms that may suggest a medical etiology. Additional clues can be found in the **attributability** and **timing** of symptom onset. As a word of caution, be mindful to not confuse a normal grief reaction to being diagnosed with an illness like cancer (which would be considered in the realm of normalcy or adjustment disorder) with the **severe** and **non-reactive** symptoms of major depressive disorder.

PREMENSTRUAL DYSPHORIC DISORDER

Premenstrual dysphoric disorder (sometimes abbreviated PMDD) is a cluster of physiological and psychological symptoms, including low mood, irritability, anxiety, fatigue, and various somatic symptoms, that occurs in some women. The symptoms of premenstrual dysphoric disorder overlap with those of clinical depression quite a bit, but the diagnostic key is the **menstrual pattern** to symptoms. Specifically, mood symptoms often begin in the luteal phase and end soon after menstruation begins. On average, symptoms last six days but can last up to two weeks. Premenstrual dysphoric disorder is not mutually exclusive with depression, as some people will have both discrete episodes of depression in addition to premenstrual dysphoria (in which case the existing symptoms of depression often get significantly worse prior to menses). Asking your patients to complete a mood chart for at least a month can help to confirm the diagnosis (although often patients will know on their own that their symptoms have a clear relationship with their menstrual cycle). Once the diagnosis is reached, treatment options can include antidepressant medications and/or psychotherapies like CBT, which have both been found to be effective.

BORDERLINE PERSONALITY DISORDER

Borderline personality disorder is a complex syndrome defined by unstable emotions, a poor sense of self, and volatile interpersonal relationships. It is the most commonly encountered personality disorder in clinical settings, and we will discuss it at length in Chapter 15. Despite how common it is, borderline personality disorder is frequently overlooked as an explanation for mood symptoms.

Mood symptoms in borderline personality disorder are characterized primarily by two features: **affective lability** and **chronic dysphoria**. Affective lability refers to rapid changes in emotional expression. In contrast to the mood episodes seen in clinical depression or bipolar disorder which often last for weeks or months, affective instability results in emotional changes within a matter of **minutes or hours**. For example, someone with borderline personality disorder may switch from joyous laughing to furious screaming within the span of 60 seconds. These changes in affect are often precipitated by external events (such as threats of abandonment), making mood notably **reactive** (rather than non-reactive as in major depressive disorder).

In addition to affective instability, people with borderline personality disorder often experience chronic dysphoria that can be mistaken for depression. The key difference is that clinical depression occurs in discrete episodes lasting months or even up to a year, whereas chronic dysphoria often persists for **years or decades**. Chronic dysphoria also needs to be distinguished from the chronic low-level depressive symptoms seen in dysthymia, which are similarly non-episodic in nature. The key lies in the difference between **dysthymia** and **dysphoria**. Dysthymia is a low-grade depression, whereas dysphoria is a state of profound dissatisfaction and disappointment with one's self and one's life. This is admittedly a difficult distinction

to make, but the easiest way to keep it straight is to think that dysthymia is how you feel after someone *dies* (as in the grieving process) while dysphoria is how you feel after someone *breaks up* with you. Both are painful and difficult to experience, but dysphoria involves feelings of rejection and questioning of self-worth that typically aren't present during grief. Pay attention to the "flavor" of sadness that your patient is reporting to help distinguish between dysthymia and dysphoria.

Recognizing the presence of borderline personality disorder when assessing a patient with depression is important, as it drastically changes the approach required for successful treatment options. Attempting to treat depression in a patient with borderline personality disorder is an exercise in futility, as traditional antidepressant medications do little to help. Instead, treatment of borderline personality disorder itself must take first priority. Treatment involves specific forms of therapy such as **dialectical behavior therapy** (DBT) that specifically address the unique symptom patterns of the disorder. Because of this, **poor treatment responsivity** can be diagnostically helpful (as can **lability** and **lack of episodicity**).

SCHIZOPHRENIA

Schizophrenia is a disorder characterized by a mixture of dramatic positive symptoms (including paranoid delusions, auditory hallucinations, and thought disorganization) as well as more subtle negative symptoms (such as lack of motivation, flat affect, poor energy, social isolation, and poverty of thought). At first, the bizarre symptoms of psychosis can seem a world away from the more recognizable syndrome of depression. However, it's not uncommon for schizophrenia to be mistakenly diagnosed as depression, as the negative symptoms of schizophrenia can strongly resemble the neurovegetative symptoms found in depression (especially in early stages of the disorder before the more dramatic positive symptoms emerge).

The relationship between depression and psychosis is complicated further by the fact that depression, bipolar disorder, schizophrenia, schizoaffective disorder, and even borderline personality disorder can all feature a mixture of mood and psychotic symptoms, yet each is a distinct disorder with separate treatment considerations. We will discuss the relationship between mood and psychotic disorders at some length in Chapter 7, but in the meantime, try to focus on *process over content* when trying to differentiate depression from schizophrenia. People with psychotic depression often have relatively preserved functioning between mood episodes, whereas people with schizophrenia often have **progressive deterioration** of functioning even during periods when symptoms are not active.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by chronic inattention and hyperactivity. It often begins in childhood, but for some it persists into adult life as well. For some, the social difficulties and low occupational attainment that often occur in untreated ADHD can lead to a sense of frustration, dissatisfaction, and helplessness which can often be misdiagnosed as depression. In these cases, the mood symptoms should improve with adequate treatment of ADHD. In cases where it does not, consideration of a separate diagnosis of depression may be warranted (as it is absolutely possible to have both depression and ADHD at the same time).

In other cases, the inattention seen in depression can be misdiagnosed as ADHD, although the episodic nature of depression should help to separate it from the **chronic** inattention seen in ADHD. In these cases, treatment of depression should naturally improve concentration.

POST-TRAUMATIC STRESS DISORDER

Post-traumatic stress disorder (PTSD) is a syndrome of cognitive and behavioral symptoms that begins following exposure to a life-threatening or violent event. There is significant overlap in symptoms between depression and PTSD, as both feature **anhedonia, sleep disturbance, and difficulty concentrating**. However, despite this overlap, depression and PTSD should be conceptualized as two distinct conditions. Depression is not a “natural effect” of experiencing trauma, and people who meet criteria for both PTSD and depression experience more distress and have worse functional outcomes than people with either diagnosis alone. In addition, there are distinct biological profiles associated with each, suggesting two separate processes (even if they do overlap in some ways). While psychotherapy and/or antidepressants can be helpful for both depression and PTSD, a more trauma-focused therapy is often necessary for successful treatment of PTSD.

ANXIETY DISORDERS

Anxiety disorders are characterized by excessive worrying. They are often comorbid with depression, with up to 60% of people with depression also having an anxiety disorder. Ignoring the presence of anxiety in a person with depression is more of a *missed* diagnosis than a *misdiagnosis*. Luckily, the same treatments are helpful in both disorders, including antidepressant medications and psychotherapies like CBT.

DEMENTIA

The term “dementia” refers to a group of neurocognitive disorders that all involve a **progressive decline in cognitive abilities** such as memory and complex thinking. In the elderly, severe depression can be mistaken for dementia, and people with depression may even score poorly on objective tests used to diagnose dementia. The term “pseudodementia” has been coined to describe patients who appear to have dementia. A prior history of depressive episodes, the presence of other symptoms of depression, and a *lack of effort* on cognitive tests (as opposed to an *inability* to engage) can all point towards a diagnosis of pseudodementia. In addition, patients with pseudodementia often have insight into their cognitive problems (“I’m losing my memory”) while those with dementia do not. Identification of pseudodementia is critical, as depression is a highly treatable condition (dementia much less so).

DISSOCIATION

As mentioned previously, feelings of depersonalization and/or derealization are seen commonly in depression even though they aren’t formally included in the DSM criteria for diagnosis. Dissociative disorders and depression are highly comorbid, and it is possible to have both at the same time. When dissociative symptoms are present, they tend to predict a worse response to conventional treatments. However, dissociative symptoms that occur *only* in the context of a depressive episode should not necessarily warrant a separate diagnosis of a dissociative disorder.

PUTTING IT ALL TOGETHER

If depression is an illness with many faces, you will need to be able to recognize each one to be able to arrive at the correct diagnosis. The differences in signs and symptoms between the various syndromes that can all present as “depression” can be slight, yet the prognosis and treatment response associated with each can be worlds apart. Because of this, a diagnosis of depression should be given cautiously and only after careful consideration of alternative explanations. Use the mnemonic **SIGECAPS** to remember the core signs and symptoms of depression at a single moment in time. The phrase “**two blue weeks**” can help you to recall the diagnostic timeframe. Major depressive disorder is notably a **non-reactive** and **episodic** disorder, with episodes typically lasting 6-12 months without treatment and 3-6 months with treatment. Treatment consists of therapy and/or antidepressant medications, either alone or in combination.

A variety of distinct clinical entities, including atypical, melancholic, postpartum, psychotic, catatonic, and seasonal depression, all should be considered various subtypes of depression but must still be recognized due to the implications they carry for treatment. In contrast, there are many misdiagnoses and missed diagnoses that may present with similar symptoms but ultimately should *not* be considered as a form of major depressive disorder. Use the **Reactive PLANETS** framework to guide your clinical judgment whenever you encounter someone presenting with problems related to mood. These questions can help you to spot when the patient’s presentation differs significantly enough from “textbook” depression for consideration of an alternative explanation.



REVIEW QUESTIONS

1. A 23 y/o F comes to a psychiatrist's office for evaluation of performance anxiety. She is a graduate student in piano performance and has heard that propranolol can be a helpful medication for this. Wanting to be thorough, her psychiatrist conducts a psychiatric review of systems. To rule out depression, the psychiatrist asks about her mood, which she describes as "normal." What is the best next question to rule out a diagnosis of a current major depressive episode?
 - A. "How is your sleep?"
 - B. "Were you abused as a child?"
 - C. "Do you enjoy things like you normally do?"
 - D. "How is your appetite?"
 - E. "Do you have thoughts that you would be better off dead?"
2. A 36 y/o M is seen for an initial psychiatric evaluation. He reports that since he was fired from his job 6 months ago, he has been spending all day in bed due to an inability to sleep at night and severe fatigue during the day. He has two children under the age of 3, and finances are becoming tight. He says, "I know I need to be looking for a job to take care of my wife and kids, but I just *can't*." His wife recently has taken to calling him "worthless," and he says, "After hearing it enough times, I find it hard to disagree." He is worried that his wife will divorce him and that his friends will leave him, saying, "Everyone just looks angry or disappointed at me all the time." When asked about his food intake, he reports that he has been eating only a bowl of cereal each day. He denies use of alcohol or any other substances. He has feelings of hopelessness but no thoughts of suicide. On exam, he moves and talks noticeably slower. Without treatment, how much longer would these symptoms be expected to continue?
 - A. Less than 1 month
 - B. Between 1 and 6 months
 - C. Between 6 and 12 months
 - D. More than 1 year
 - E. These symptoms will likely continue until treatment is started
3. (Continued from previous question.) The psychiatrist recommends starting the antidepressant sertraline along with CBT. That night, the patient takes his first dose of the medication. Which of the following symptoms is likely to resolve first?
 - A. Finding it hard to disagree when his wife calls him "worthless"
 - B. Spending all day in bed
 - C. Eating only a single bowl of cereal each day
 - D. Moving and talking noticeably slower
 - E. Feeling that everyone looks angry or disappointed at him
 - F. All of these symptoms are equally likely to respond first

4. (Continued from previous question.) The patient returns to see his psychiatrist several times over the next few months. By the fourth month, he reports that his mood is entirely back to normal. The decision is made to continue both CBT and sertraline for another year. One year later, he is successfully tapered off of medication with no return of depressive symptoms. The patient says, "That was the worst few months of my life, but I'm glad it's over. I hope nothing like this ever happens again." What is this patient's risk of experiencing another episode in the future?
- A. 100% (it is certain that he will have another episode)
 - B. Between 50 and 100% (it is more likely than not)
 - C. 50% (it is equally likely and unlikely)
 - D. Between 0 and 50% (it is less likely than not)
 - E. 0% (it is completely unlikely)
5. A 47 y/o F who works as a business executive presents to a psychiatrist reporting worsening mood symptoms over the past four weeks, including depressed mood, irritability, feeling cold all of the time, difficulty sleeping, lack of energy, poor appetite, and constipation. She normally enjoys trail running but has not been able to exercise for more than a few minutes at a time for the past two months. Despite eating very little, she says that she has gained more than 15 lbs. over this same time period. She says, "My sister has suffered with depression as well and says that fluoxetine works really well for her. I was wondering if I could go on that too." Which of the following is the next best step?
- A. Prescribe fluoxetine
 - B. Refer for CBT
 - C. Prescribe fluoxetine along with a referral for CBT
 - D. Order laboratory testing
 - E. Reassure the patient that her symptoms are normal
6. A 72 y/o F sees her primary care doctor for the first time in over a decade. She says that her husband of over 50 years suffered a stroke two months ago that left him "basically like a vegetable." The patient now spends most of her time caring for her husband, which leaves her feeling exhausted and depressed. She thinks constantly about what it would mean if her husband were to die, although she also admits that "sometimes I think it would be good for him to go, which makes me feel like a horrible person." She denies feeling hopeless or having thoughts of suicide. Her appetite and concentration are intact. Which of the following is the next best step?
- A. Refer for therapy
 - B. Reassure the patient that her symptoms are normal
 - C. Discuss risks and benefits of medications
 - D. Provide referrals to social resources such as caregiver support
 - E. All of the above

1. **The best answer is C.** In addition to a sense of depressed mood, asking about anhedonia is a highly sensitive marker for ruling out depression. Someone who denies both a depressed mood and anhedonia is exceedingly unlikely to be currently in a major depressive episode. The other questions may be important to ask to get a better sense of the patient's current mental state (especially suicide, answer E) but are not as sensitive for ruling out a major depressive episode.
2. **The best answer is B.** This patient is likely suffering from major depressive disorder (although other causes cannot be entirely ruled out at this time). The average length of an untreated depressive episode is between 6 and 12 months. Given that he has already had symptoms for 6 months, it is most likely that his symptoms will last up to another 6 months (ruling out answers A, C, and D). As an episodic disorder, the symptoms of depression are unlikely to continue indefinitely even if treatment is not started (answer E).
3. **The best answer is E.** The core symptoms of depression, including feelings of worthlessness (answer A), fatigue (answer B), poor appetite (answer C), and psychomotor retardation (answer D) are all unlikely to respond to antidepressant treatment within a single day. In contrast, antidepressants have been shown to reduce negative affective biases even within the first day of treatment, suggesting that this patient's feelings that others look angry or disappointed will resolve first.
4. **The best answer is C.** Around 50% of people with a first episode of depression will have an isolated episode, while the other 50% will develop recurrent major depressive disorder.
5. **The best answer is D.** While the patient reports symptoms consistent with depression, there are also other symptoms that suggest a medical etiology, including cold intolerance, constipation, an inability to exercise, and significant weight gain in the absence of food intake. The most likely explanation is untreated hypothyroidism, which would need to be confirmed with laboratory testing. Treating her symptoms with antidepressants or CBT (answers A, B, and C) would not be appropriate until hypothyroidism has been ruled out. She should not be reassured that her symptoms are normal when there is evidence of likely medical pathology (answer E).
6. **The best answer is E.** This patient is likely suffering from adjustment disorder given the recent major life change and resulting symptoms of depression that do not meet criteria for a full disorder. Adjustment disorder is a "diagnosis of normalcy," so reassurance should be given (answer B). Treatment for adjustment disorder includes supportive therapy (answer A), with referrals to social support when indicated (answer D). It is reasonable to have a discussion about the risks and benefits of medications even if the risks likely outweigh the benefits in this case (answer C).