

## Major Depressive Disorder (MDD, Depression) — Definition and Treatment

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**Major depressive disorder (MDD) is a unipolar mood disorder characterized by persistent low mood and loss of interest in association with somatic symptoms. The overall incidence of the disease is 6.7 % with prevalence increasing with age. Monoamine oxidase deficiency and amine neurotransmission abnormalities are the incriminated causes of the disease. Psychotherapy, pharmacotherapy and electroconvulsive therapy (ECT) are the modalities used to treat the disease. Its leading cause of mortality is suicide, which is more common among the elderly population.**



### Definition

Depression is a **unipolar mood disorder characterized by persistent low mood and loss of interest** in daily living activities. It is associated with somatic symptoms, such as weight loss, insomnia, and decreased energy. It is also known as major depressive disorder (MDD). The disorder affects one's thoughts and actions leading to the inability to perform daily duties.

It should be **differentiated from normal occurrences of grief and sadness** based on the following criteria:

- Grief following the loss of a close person waxes and wanes and **lasts for a shorter duration**. In major depressive disorder, however, patients experience the symptoms for more than two weeks.
- The individual with depression has a complete **feeling of worthlessness and**

**loss of self-esteem.** A sad individual, or one undergoing a period of grief, does not feel worthless.

## Epidemiology of Depression

In 2015, an estimated 16.1 million adults, or 6.7% of the adult population, in the United States had experienced at least one episode of depression within the previous year. It is also thought to be twice as common in women than men due to hormonal and psychosocial differences.

The **incidence of depression is highest between the ages of 20 and 40 years.** A study on the nature of presenting illness showed that depression represented 12% of all new illnesses and 45% of all mental illnesses.

The numbers worsen with age; the prevalence of depression among those older than 65 years of age is 15%. The disease also accounts for 50% of mental illnesses among the elderly. Suicidal ideation and somatic presentation are more widespread in this age group compared to others.

## Classification of Depression

**The Diagnostic and Statistical Manual (DSM) classifies major depressive disorder as major depressive episodes (MDE) with:**

- Psychotic features, such as hallucinations and delusions
- Feelings of low self-esteem and guilt
- Psychomotor changes, such as decreased efficiency, difficulty concentrating, or fatigue
- Sleep disturbances, which can manifest as hypersomnia or insomnia
- Unintentional weight gain or loss
- Chronic course greater than two years
- Postpartum onset
- Seasonal occurrence

The DSM classifies depression based on various categories and specifications that can become very complex. A simpler classification is the proposed two-dimensional system, one of chronicity and one of severity.

### The chronicity axis

1. No past history of depression
2. Prior history of a depressive episode lasting less than two years
3. Recurring episodes of depression that last less than two years with phases of remission
4. Prior history of a depressive episode lasting more than two years without phases of remission

### The severity axis

1. No depressive symptoms
2. Subthreshold (2—4 symptoms)
3. Mild (5—6 symptoms with mild functional impairment)
4. Moderate (symptoms and functional impairment between mild and severe)

5. Severe (8–9 symptoms and severe functional impairment)

## Pathophysiology of Depression

The cause of the disease is not well elucidated. However, it is associated with several risk factors, or causative mechanisms, that eventually lead to altered behavior and cognition.

A major depressive disorder is more common among monozygotic twins (75 %) than dizygotic twins (14–19 %), suggesting that the disease has some genetic influence.

Biological causes, such as neuroendocrine malfunction, lead to decreased levels of neurotransmitters, such as serotonin, which control mood and behavior. The low levels of hormones cause depression.

Cognitive distortions cause a negative perception of the world and make some people more susceptible to environmental stressors. These individuals believe they have no control over these circumstances.

Early childhood interpersonal losses may be a risk factor for the causation of the disease because these patients experience increased occurrences of the disease.

### **Other risk factors include:**

- Poor familial and social relationships
- Dependent personality disorder
- People with personality disorders such as social isolation habits

### **The risk factors act synergistically to cause the disease in any of the following pathways:**

## Monoamine oxidase deficiency theory

Environmental influences cause genetically predisposed individuals to develop abnormalities in amine neurotransmission, which mediates depressive states. Nerves that contain noradrenaline and 5-hydroxytryptophan are impaired; thus, there is no transmission. These neurotransmitters are the main regulators of mood, attention, sleep, appetite, and cognition. With reduced transmission, the patients are tipped into depressive states, insomnia, and reduced appetite and interest.

## Stress hormones and cytokines

Calcitonin is a hormone that is produced in a stressful situation, and studies have shown patients with depression have altered calcitonin levels. As a result, pituitary corticotrophin hormone is released, which triggers the release of cortisol into the circulation, thus mediating depression.

## Neuroanatomic theory

Evidence-based literature associate structural and functional abnormalities in the prefrontal cortex with depression. The nerves that transmit messages involved in mood and behavior are destroyed, leading to the disease. The theory is supported by the improvement of patients who undergo deep brain stimulation and evidence gathered during neuroimaging and post-mortem examinations.

## Neurotrophic hypothesis

Untreated depression leads to neurotrophic damage to the hippocampus and increases sensitivity to stress factors. The damage is thought to arise from glutamine and glucocorticoid toxicity. This theory is supported by the fact that the recurrence rate of depression increases as the number of recurrent episodes increases, mainly due to further damage with each episode.

## Clinical Features of Depression

A major depressive disorder is diagnosed if a patient has evidence of one episode of depression and does not meet the criteria for bipolar disorder or substance-induced mood disorder.

**An episode of depression as per DSM-IV is characterized by at least five of the following criteria:**

- Depressed mood for the larger part of the day
- Insomnia or hypersomnia
- Feeling of worthlessness
- Decreased or lost interest in activities
- Decreased levels of concentration
- Increased or decreased appetite
- Psychomotor agitation
- Suicidal ideation and/or attempts

To fulfill the criteria, the symptoms must include depressed mood or loss of interest and must be present for at least two weeks.

**The following groups of symptoms characterize major depression:**

### Affective Symptoms

Patients are in a depressed mood during the day and display this by being sad and always expressing displeasure on simple things that happen. Their symptoms may also manifest physically with tearing and irritability, especially in children. Pleasurable events and hobbies are no longer enjoyable to them, and they may have anxiety or nervousness during certain activities.

### Vegetative

Those suffering from depression go to bed while in deep thought, thus finding it difficult to sleep. The most common scenario is waking up in the middle of the night or very early in the morning and being unable to get back to sleep. They may also present with excessive sleep after periods of sleep deprivation.

### Motivational

**Loss of interest** in usual activities, especially hobbies and sexual activity, are common. The patients view themselves as poor in those activities and do not want to be assessed.

Suicidal thoughts or acts indicate a culminated loss of interest in life in general.

## Cognitive

These patients have negative self-reflection and view themselves as useless. They then develop a sense of guilt and low self-esteem. This leads to a diminished ability to think and concentrate on various activities.

## Somatic

General complaints include weight loss due to persistent loss of appetite and interest in feeding.

## Investigations of Depression

Laboratory investigations are done mainly to rule out other medical conditions and as a baseline before initiation of therapy. **They include:**

1. Full hemogram with an erythrocyte sedimentation rate (ESR)
2. Renal function tests
3. Liver function tests
4. Thyroid function tests
5. Enzyme assays, such as dexamethasone suppression tests and adrenocorticotrophic hormone (ACTH) stress test

Neuroimaging methods are used to identify any organic disease and study neuroanatomy for possible etiologies of depression. **The best imaging modalities are:**

1. Computed Tomography (CT) scan of the brain
2. Magnetic Resonance and Imaging (MRI) scans
3. Positron Emission Tomography (PET) scans have also been used to study receptor binding within the brain and assess the function

## Differential diagnosis of Depression

<b>Dysthymic disorder</b>	A unipolar mood disorder with a similar history of longstanding low mood but does not meet the criteria for a major depressive disorder.
<b>Schizophrenia</b>	Psychotic diseases with negative symptoms that may mimic depression.
<b>Bipolar disorder</b>	Patients suffering from bipolar disorder will eventually meet the criteria for a major depressive disorder. While patients with depression have a hypomanic phase between depressive episodes, patients suffering from bipolar disorder have a manic phase.
<b>Bereavement</b>	Patients will have a similar presentation of mood alteration. Bereavement lacks functional impairment and rarely lasts beyond two months.
<b>Dementia</b>	The lack of concentration that comes with the loss of memory may suggest depression. The disease lacks other symptoms of depression.

<b>Parkinson's disease</b>	This is a disorder that can be secondary to an identifiable general medical condition and presents with altered mood.
<b>Mood disorders secondary to substance</b>	Change of mood may occur in the presence of an identifiable trigger such as abuse of alcohol.

## Treatment of Depression

### Psychotherapy

It is the treatment of choice for mild disease and is mainly undertaken in an outpatient setting. The forms of psychotherapy include supportive therapy, cognitive-behavioral therapy, and brief interpersonal therapy.

### Pharmacotherapy

It is indicated for moderate to severe disease that requires hospital admission during the acute phase of treatment. Pharmacotherapy may lead to undesired effects of sedation, sexual dysfunction, vomiting, insomnia, and hypertension.

#### **Tricyclic antidepressants (TCAs) such as Amitriptyline and Clomipramine**

They are the first-line agents for managing major depressive disorder due to their response rate but are associated with dangerous adverse effects, such as sedation and anticholinergic effects.

#### **Selective serotonin reuptake inhibitors (SSRIs) such as sertraline (Zoloft) and Citalopram (Celexa)**

They are used as first-line agents to treat a major depressive disorder in patients who are refractory to TCAs. Common side effects include gastrointestinal upset, sexual dysfunction, and insomnia.

#### **Monoamine oxidase inhibitors (MAOIs) such as Phenelzine**

They are second-line agents. The disadvantages of this class of drugs are their association with orthostatic hypotension and dietary associated hypertension.

#### **Atypical antidepressants**

Bupropion is also used due to its lower rate of sexual dysfunction occurrence. However, it requires multiple dosing. Venlafaxine is associated with elevated blood pressure due to noradrenaline inhibition.

#### **Mood stabilizers and antipsychotics**

Drugs such as lithium are used in combination with antidepressants in patients who present with anxiety. They also help reduce recurrence rates.

### Combination therapy

A combination of psychotherapy and pharmacotherapy is more effective in the treatment of a major depressive disorder.

## Electroconvulsive therapy (ECT)

ECT is a safe and effective method of treatment, especially for patients whose symptoms no longer respond to pharmacotherapy. The modality is reported to have a 90% response rate. It is the treatment of choice in:

- Severe depression
- Patients with psychosis
- Patient with contraindications to antidepressants, such as advanced age
- A disease that is refractory to other methods of treatment

Cardiac monitoring is initiated, airway secured and the following drugs are administered:

1. A short-acting anesthetic agent
2. A short-acting muscle relaxant
3. Atropine

A rubber mouth block is placed and an electrical stimulus is introduced in the temporal and occipital aspect of the head.

The impulse delivered to the brain during electroconvulsive therapy may cause headaches as well as anterograde or retrograde amnesia.

## Complications of Depression

If the disease progresses untreated, then neurotrophic brain damage occurs, which leads to higher rates of recurrence.

**Suicidal attempts and acts are also seen with untreated disease**, and they are the most common causes of death in depression.

## Course and Prognosis of Depression

Without treatment, depressive episodes last for about 6–13 months, while treatment reduces the time to < 3 months. Patients who have had a depressive episode have a 50% chance of recurrence, which rises to 70% after the second episode and 90% after the third. Recurrent episodes tend to last 4–16 weeks.

A 15% mortality rate is seen among patients; the main cause is suicide. Indicators of bad prognosis are a severe disease that warrants hospital admission, multiple episodes, residual symptoms, comorbid psychiatric conditions such as substance abuse and low confidence level, and social dysfunction. Good prognostic indicators include mild disease, the absence of psychotic symptoms, advanced age, and acute onset.

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