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 association with somatic symptoms such as weight loss, difficulty in sleeping and decreased energy. It is also known as major depressive disorder (MDD). The disorder affects one’s thoughts and actions leading to 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 only 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 self-esteem is lost in its entirety, while in a sad individual, or one undergoing
Epidemiology of Depression

It is reported that in the year 2015, 16.1 million adults in the United States experienced at least one episode of depression within the year. This represented a 6.7 % prevalence. It is also thought to be twice as more common in women than men due to hormonal and psychosocial differences.

The incidence of depression increases between the age of 20–40 years and decreases after 65 years of age. 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 rampant in this age group compared to others.

Classification of Depression

The diagnostic and statistical manual for mental illnesses classifies depression based on various categories and specifications. With each edition and further research the categories and specifications become more complex, begging for a simpler classification of the disease. One such classification is the proposed two-dimensional system that entails a dependence of chronicity and severity axis.

DSM classifies major depressive disorder as major depressive episodes (MDE) with:

- Psychotic features such as hallucinations and delusions
- Melancholic features of symptom worsening in the morning, guilt and psychomotor retardation
- Atypical features such as increased sleep and weight gain
- Chronic course greater than two years
- Postpartum onset
- Seasonal occurrence

The system improves severally with time and is noted to revolve around the proposed two-dimensional system that is made up of:

The chronicity axis

1. No history of depression in the past
2. Prior history of a depression episode lasting less than 2 years
3. Recurrence episodes of depression that last less than 2 years and are accompanied by phases of remission
4. Prior history of a depression episode lasting more than 2 years without episodes of remissions

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.

Major depressive disorder is more common among monozygotic twins (75 %) as compared to dizygotic twins (14—19 %). This has led to the theory that the disease has some genetic influence.

Biologic causes such as neuroendocrine malfunction lead to the decrease in the level of neurotransmitters that control mood and behavior such as serotonin. The low levels of hormones cause depression.

Cognitive distortions cause a negative perception of the world and render someone susceptible to stresses in the environment. These individuals believe they have no control over environmental stressors.

Early childhood interpersonal losses have been postulated to be a risk factor for causation of the disease as these patients experience an increased occurrence of the disease.

**Other risk factors for the disease include:**

- Poor familial and social relationships as in single individuals
- Females who have extreme dependency habits
- 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**

Genetically predisposed individuals with environmental influence cause abnormalities in amine neurotransmission which mediate depressive states. Noradrenaline and 5-hydroxytryptophan containing nerves are impaired and thus there is no transmission. These nerves 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 releasing hormone is produced in a stressful situation and is a risk factor for the disease. 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 concurs that structural and functional abnormalities in the prefrontal cortex are associated with depression. The nerves that transmit messages involved in mood and behavior are destroyed leading to the disease. The theory is supported by improvement of patients with 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 more damage with each episode.

Clinical Features of Depression

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
- Decrease or loss of interest in activities
- Decreased level of concentration
- Increase or decrease in 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. They may also manifest physically with tearing and irritability, especially in children. Pleasurable events and hobbies are no longer fun to them, and they may have anxiety and are sweaty during certain activities.

Vegetative

Those suffering from depression go to bed while in deep thoughts, thus find it difficult to sleep. The most common scenario is waking up in the middle of the night or very early in the morning 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, more so 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 indicated a culminated loss of interest in life in general.
Cognitive

These patients have a 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 ESR
2. Renal function tests
3. Liver function tests
4. Thyroid function tests
5. Enzyme assays such as dexamethasone suppression tests and 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. PET scans have also been used to study receptor binding within the brain and assess function

Differential diagnosis of Depression

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Dysthymic disorder</strong></td>
<td>A unipolar mood disorder with a similar history of longstanding low mood but does not meet the criteria for a major depressive disorder.</td>
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<tr>
<td><strong>Schizophrenia</strong></td>
<td>Psychotic diseases that have negative symptoms that may mimic depression.</td>
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<tr>
<td><strong>Bipolar disorder</strong></td>
<td>Patients suffering from bipolar disorder will eventually meet the criteria for a major depressive disorder. While depression patients have a hypomanic phase between the episodes of depression, patients suffering from bipolar disorder have a manic phase.</td>
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<td><strong>Bereavement</strong></td>
<td>Patients will have a similar presentation of mood alteration. Bereavement lacks functional impairment and rarely lasts beyond 2 months.</td>
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<tr>
<td><strong>Dementia</strong></td>
<td>The lack of concentration that comes with the loss of memory may suggest depression. The disease lacks other symptoms of depression.</td>
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<tr>
<td><strong>Parkinson’s disease</strong></td>
<td>This is a disorder that can be secondary to an identifiable general medical condition and presents with altered mood.</td>
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Mood disorders secondary to substance

| Mood disorders secondary to substance | Change of mood may occur in 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 the 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 in the acute phase of treatment.

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

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

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

They are used as first-line agents in the treatment of major depressive disorder or 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. Disadvantages of this class of drugs is 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 elevation of 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 are also important in the reduction of recurrence rates.

Combination therapy

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

Electroconvulsive therapy (ECT)

It is a safe and effective method of treatment. 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
- 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.

Complications of Depression

If the disease progresses untreated, then neurotrophic brain damage occurs that leads to higher rates of recurrence if resolution does not occur.

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

Pharmacotherapy may lead to undesired effects of sedation, sexual dysfunction, vomiting, insomnia and hypertension.

The impulse delivered to the brain during electroconvulsive therapy may cause headaches, anterograde and retrograde amnesia.

Course and Prognosis of Depression

Without treatment, the episodes of depression last for about 6-13 months, while with treatment the time reduces to < 3 months. Patients who have had an episode of depression have a 50 % chance of recurrence, which rises to 70 % after the second episode and 90 % after the third. The recurrent episode is always shorter lasting, from 4-16 weeks.

A 15 % mortality rate is seen among patients, with the main cause being suicide. Indicators of bad prognosis are a severe disease that warrants 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.

References


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