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Depression: A comprehensive review of pathophysiology, epidemiology, types and management

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Abstract
Depression is one of the most common and disabling mental disorders worldwide and represents a major public health concern. It is characterized by persistent sadness, loss of interest in activities, reduced energy and disturbances in sleep, appetite and cognitive function. According to the World Health Organization, depression is a leading cause of disability and contributes significantly to global disease burden and suicide mortality. The aetiology of depression is complex and involves interactions between genetic, biological, psychological and environmental factors. Several hypotheses explain its pathophysiology, including the monoamine hypothesis, inflammatory hypothesis, endocrine dysfunction of the hypothalamic-pituitary-adrenal axis, neurotrophic alterations involving brain-derived neurotrophic factor and imbalance of glutamatergic and GABAergic neurotransmission. Structural and functional changes in brain regions such as the prefrontal cortex, hippocampus and amygdala are also associated with depression. Management strategies include antidepressant medications, psychotherapy and emerging treatments such as ketamine therapy and transcranial magnetic stimulation. This review summarizes the epidemiology, mechanisms, types and current management approaches of depression.

Keywords: Depression, Pathophysiology, Epidemiology, Antidepressant therapy, Monoamine hypothesis, Neurotransmitters, HPA axis, Brain-derived neurotrophic factor, Psychotherapy.

Introduction

Depression is a mental disorder characterized by episodes of persistent depressed mood lasting more than two weeks, accompanied by symptoms such as disturbed sleep and appetite, impaired concentration, excessive guilt, suicidal ideation, loss of interest or pleasure and reduced energy or fatigability.

Major depressive disorder significantly impairs daily functioning and is associated with reduced quality of life, decreased productivity and substantial economic burden on both patients and society. Mental health disorders result in substantial health loss and human suffering worldwide. According to the World Health Organization, depression is the leading cause of global disability, accounting for approximately 7.5% of all years lived with disability. It is also a major contributor to suicide mortality, with nearly 800,000 deaths reported each year. The global prevalence of mental health disorders continues to rise, particularly in low- and middle-income countries [1].

In 2019, about 1 in 8 people worldwide (970 million) had a mental disorder, with anxiety and depression being the most common. These numbers increased sharply in 2020 due to COVID-19. In India, mental health problems are mainly due to social stigma, poor access to care, rising stress from nuclear family systems and a shortage of mental health professionals. Depression usually starts in the mid-20s, and women are almost twice as likely as men to suffer from it. It is a major cause of suicide, especially among teenagers, young adults and older people, and is also the leading cause of disability worldwide.

Depression occurs in different forms with different symptoms and causes. Selecting the appropriate course of treatment is made easier by being aware of these.

This article aims to review the current understanding of the pathophysiology of depression, explore the underlying mechanisms associated with different types of depression, and outline conventional therapies and new treatments for depression [2].

Background

Depression is derived from the Latin word *deprimere*, meaning "to press down," where *de* means "down" and *premere* means "to press." The term therefore conveys a sense of heaviness, often described as feeling "sad" or "low." [1] The concept of depression has evolved considerably over centuries, reflecting changes in medical, philosophical and scientific understanding of mental illness. In ancient civilizations, depressive symptoms were commonly described under the term *melancholia*. Hippocrates (460–370 BC) proposed that melancholia resulted from an excess of black bile, one of the four bodily humors and described symptoms such as fear, sadness, insomnia and loss of appetite. This humoral theory dominated medical thinking for many centuries and framed depression as a biological imbalance rather than a moral or spiritual failing [3]. In the 18th and 19th centuries, the term *depression* replaced *melancholia*. Doctors like Pinel, Esquirol and Kraepelin explained it as a mood disorder rather than a thinking problem. This helped establish depression as a medical psychiatric condition [4]. Normal sadness is a temporary emotional response to life events that usually fades with time and doesn't significantly disrupt daily life. In contrast, clinical depression involves persistent, intense feelings of hopelessness and lack of interest lasting weeks or longer and can severely impair daily functioning [5].

Prevalence – World scenario and Indian scenario

In India, depression is consistently identified as the most prevalent psychiatric disorder in community-based surveys. It is also among the most frequently diagnosed mental illnesses in outpatient clinics and in patients attending

medical and surgical services. Depression is common among older adults across different healthcare facilities. Indian research suggests that stressful life experiences before the illness greatly increase the risk of depression. Research on women shows that interpersonal conflicts, marital problem and sexual coercion are important risk factors and should be carefully recognized and addressed [6, 7]. More research is needed on treatment cost, patient attitudes, adherence, compliance and brain-related factors. Studies should also examine the course of depression in India to decide how long treatment should continue. In addition, low-cost and practical treatment models for primary care should be developed to improve depression care [8].

Table 1: The Indian Council of Medical research, a collaborative project at four centres (Bikaner, Goa, Patiala and Vellore) and the outcome.[9]

ICMR descriptive Categories	*Bikaner N=68 %*	*Goa N=85 %*	*Patiala N=102 %*	*Vellore N=68 %*	*All centres N=323 %*
Predominantly Depressed type	5.9	11.8	17.7	11.8	11.8

Table 2: Total population effects of different depression interventions are reported in given above Table.[10]

	Africa		**The Americas**			**Eastern Mediterranean**		**Europe**			**South-East Asia**		**Western Pacific**	
	AfrD	AfrE	AmrA	AmrB	AmrD	EmrB	EmrD	EurA	EurB	EurC	SearB	SearD	WprA	WprB
Total population (million)	294.1	345.5	325.2	430.9	71.2	139.1	342.6	411.9	218.5	243.2	293.8	1241.8	154.4	1532.9
Current burden of depression	1906	2154	5031	5589	867	1184	3507	4074	2548	2634	2832	17 123	1000	14 515

Epidemiology of Depression: Global Burden

In the world, depression is among the most prevalent mental illnesses. According to WHO (2023), about 5% of adults, or nearly 280 million people, are affected globally. It is more common in women (~6%) than men (~4%) and increases with age, affecting around 5.7% of adults over 60 years. Depression causes a major burden of disability and was the second leading cause of years lived with disability (YLDs) even before COVID-19. In 2019, major depressive disorder ranked just below low back pain as a cause of disability. The COVID-19 pandemic further increased this burden, with depression accounting for about 49.5 million DALYs in 2020. Depression is also strongly linked to suicide, which causes over 700,000 deaths annually, making it a major global public health concern.

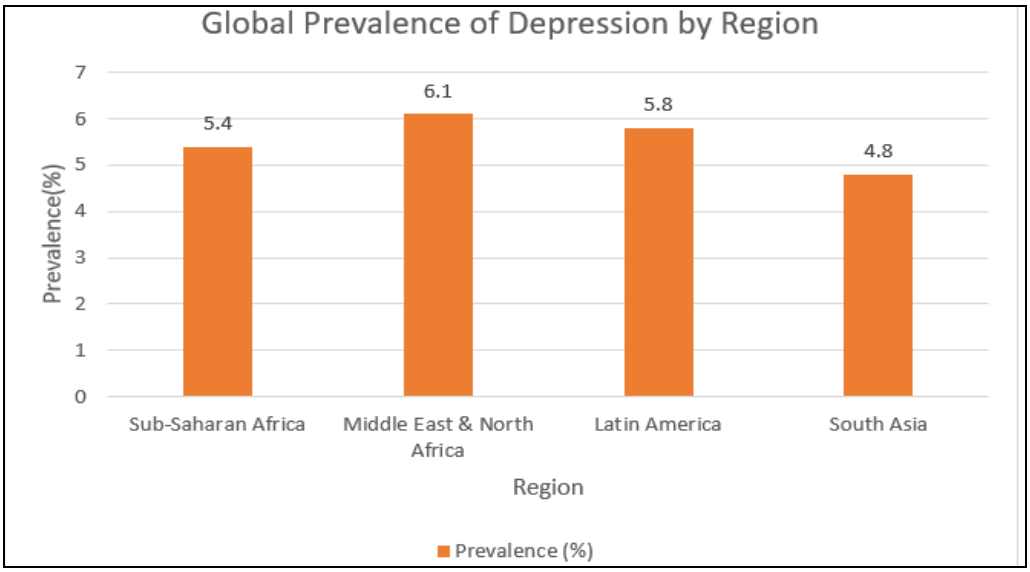

Fig 1: Prevalence of Depression Across Different Regions

The prevalence and impact of depression differ widely across regions. Higher rates are often reported in high-income Western countries and conflict-affected areas, while lower rates are seen in parts of East and Southeast Asia, possibly due to underdiagnosis or cultural influences. According to IHME (2019), mental disorders are most common in Australasia, tropical Latin America, and high-income North America, while depression burden is particularly high in Sub-Saharan Africa and North Africa–Middle East regions. Global surveys also report depression prevalence above 5% in the Middle East, Sub-Saharan Africa, and Eastern Europe, whereas countries such as Japan and South Korea report much lower rates.

Access to mental health care varies by income level, with over 75% of people in low- and middle-income countries receiving no treatment, suggesting underreporting in these regions. In Latin America and the Caribbean, depression is a major and growing cause of disability. In South Asia, recent studies show a slight decline in age-standardized incidence, possibly due to socioeconomic changes or reporting differences. Overall, depression occurs worldwide but appears more common in conflict-affected, high-stress, and some high-income regions, while East Asia generally reports lower prevalence.

Demographic Disparities

Demographic Disparities Depression affects subgroups unequally. Key patterns include:

Age

Depression affects different age groups unevenly, with onset often occurring in adolescence and peaking in young adulthood. Global data show that most depression-related disability occurs between ages 16 and 65, especially in the 25–34 age group. In the U.S., nearly one in five young adults (18–25 years) experience major depression, compared to far fewer older adults. Children and adolescents are particularly vulnerable, with mental disorders affecting about one in seven worldwide. Suicide is also a leading cause of death among young people. In contrast, older adults report comparatively lower rates of depression, highlighting the heavy burden on younger populations.

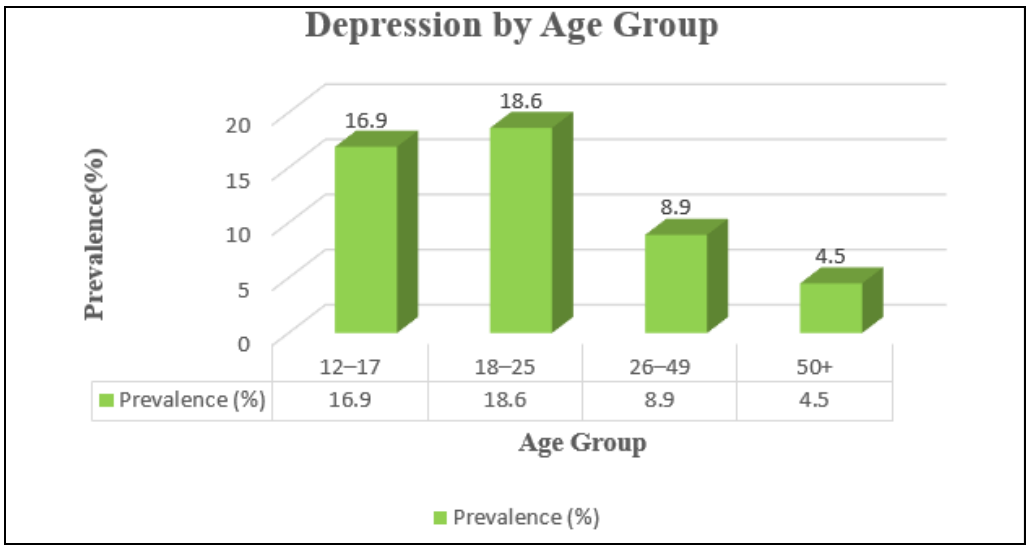

Fig 2: Depression Prevalence by Age Group

Gender and sexual/gender minorities:

Depression is significantly more common in women than men worldwide, with women experiencing about 50% higher rates. In the U.S., around 10% of women report major depression compared to about 6% of men. Factors contributing to this gap include caregiving stress, higher exposure to abuse, hormonal influences, and social roles. Pregnancy and the postpartum period are especially high-risk, with over 10% of women affected. Depression rates are also much higher among sexual and gender minorities. Studies show LGBTQ+ individuals, particularly transgender and nonbinary youth, experience depression far more often than the general population, largely due to stigma and discrimination.

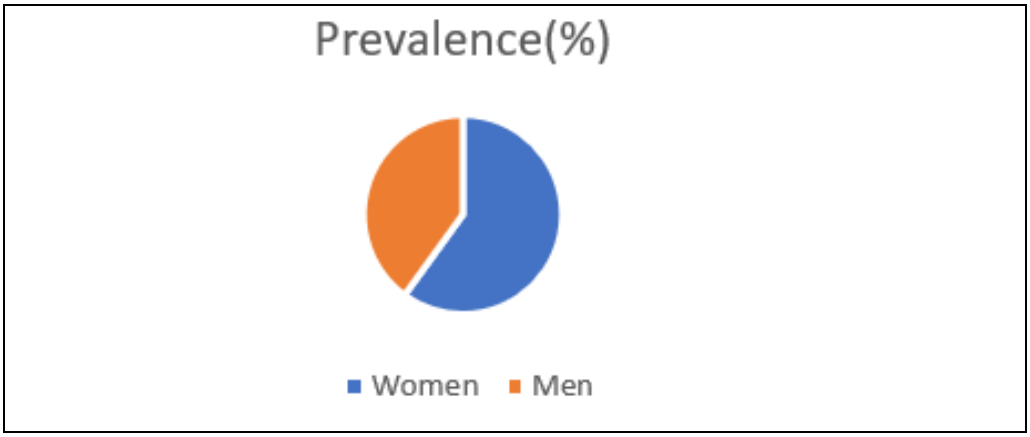

Fig 3: Prevalence of Depression by Gender

Socioeconomic status

Depression is strongly associated with low socioeconomic status, including poverty, unemployment, and income inequality. Countries with lower incomes and higher joblessness tend to report greater depression prevalence. Economic growth and strong social support systems can reduce this risk. Within nations, people with less education and lower income experience higher depression rates due to

chronic stress and poor living conditions. Limited access to mental health care further worsens outcomes. Many low-income countries spend very little on mental health services, and even in wealthy nations many people remain untreated. Overall, depression disproportionately affects socially and economically disadvantaged groups.

Race and ethnicity

Most data on depression by race and ethnicity come from high-income countries. In the U.S., highest rates are seen among people of multiple races and American Indian/Alaska Native groups, while Asian Americans report the lowest rates. White and Hispanic populations show moderate prevalence, and Black Americans slightly lower levels. These differences likely reflect social conditions, cultural influences, and access to diagnosis and care. Globally, Indigenous and minority populations often experience higher mental health burdens due to marginalization. Even after adjusting for income, disparities persist in many countries. Overall, racial and ethnic differences in depression reflect broader social inequalities. [10].

Table 3: Social Determinants of depression, Mechanisms and Supporting Evidence.

Determinant	Mechanism	Evidence (Source)
Poverty	Chronic stress, poor access to services, food/housing insecurity	Lund *et al*., 2010; Ridley *et al*., 2020
Education	Health literacy, resilience, social capital	Lorant *et al*., 2003; Cutler & Lleras-Muney, 2006
Unemployment	Suicide risk, stress, self-worth and loss of money or routine	Paul & Moser, 2009; Milner *et al*., 2013
Family dysfunction	Trauma, abuse, insecure attachment, lack of emotional support	Felitti *et al*., 1998; Kessler *et al*., 2010
Gender/Sexual Minority	Stigma, exclusion, violence	WHO, 2023; The Trevor Project, 2023
Ethnicity	Discrimination, cultural stigma, access barriers	NIMH, 2022; WHO, 2023

Signs and symptoms

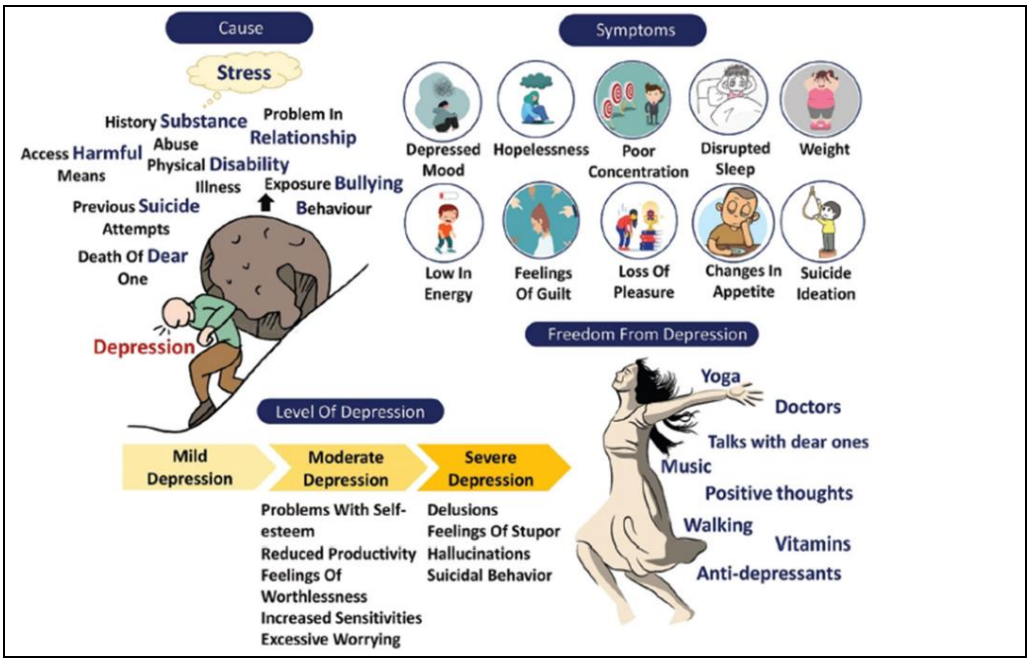

Fig 4: Signs and Symptoms of Depression

Symptoms of depression differ among individuals and are influenced by psychological, social and economic factors. Therefore, the type and severity of symptoms vary across different groups of people.

The symptoms are as follows:

a. General symptoms: These symptoms may be felt for more than 2 weeks:

1. Feeling sad, anxious or empty
- Feeling hopeless or pessimistic
- Feeling guilty, worthless or helpless
- Loss of interest in surroundings
- Trouble with concentration, memory or making decisions
- Abnormal sleeping time
- Appetite changes
- Gaining or losing weight
- Feeling restless or irritable
- Suicidal thoughts

b. Symptoms in Adults: Depression in adults, especially older adults, is often not diagnosed or treated because its symptoms resemble other illnesses. Common signs include:

- Tiredness
- Poor appetite
- Sleep problems
- Reduced interest in sex
- Dissatisfaction with life
- Boredom
- Feelings of helplessness or worthlessness
- They may prefer staying at home and avoiding social activities

- Suicidal thoughts in older adults indicate severe depression and must not be ignored
- Older men have the highest risk of suicide among depressed individuals [11, 12]

c. Symptoms in Children and Teens: Depression in children and teenagers is a serious concern. Childhood or emotional trauma can lead to depression that may continue into adulthood. Common signs include:

- Kids could decline to attend school.
- Cling to parents
- Lose confidence
- Feel fearful
- Avoid playing with others
- Teenagers with depression may seem irritable, withdrawn, misunderstood and may show negative behavior, substance use or harmful thoughts
- Teenage girls are more likely to experience depression than boys [13, 14]

d. Symptoms during Pregnancy: Pregnancy is a period when mental health changes need careful attention, mainly due to hormonal fluctuations that support foetal growth. Depression during pregnancy occurs at rates similar to those in non-pregnant women [15, 16]. Common symptoms include:

- Low self-esteem
- Hopelessness
- Poor concentration
- Reduced emotional expression
- Loss of interest
- Disturbances in sleep and appetite [17]

e. Postpartum Depression [18]

Postpartum depression involves physical, emotional, hormonal and behavioral changes after childbirth. Many first-time mothers experience mild "baby blues," but some develop more serious symptoms. These include:

- Extreme fatigue
- Disturbed sleep
- Reduced sexual interest
- Appetite changes
- Frequent mood swings
- Persistent feelings of worthlessness, helplessness and hopelessness.

Factors or Causes of Depression [19, 22]

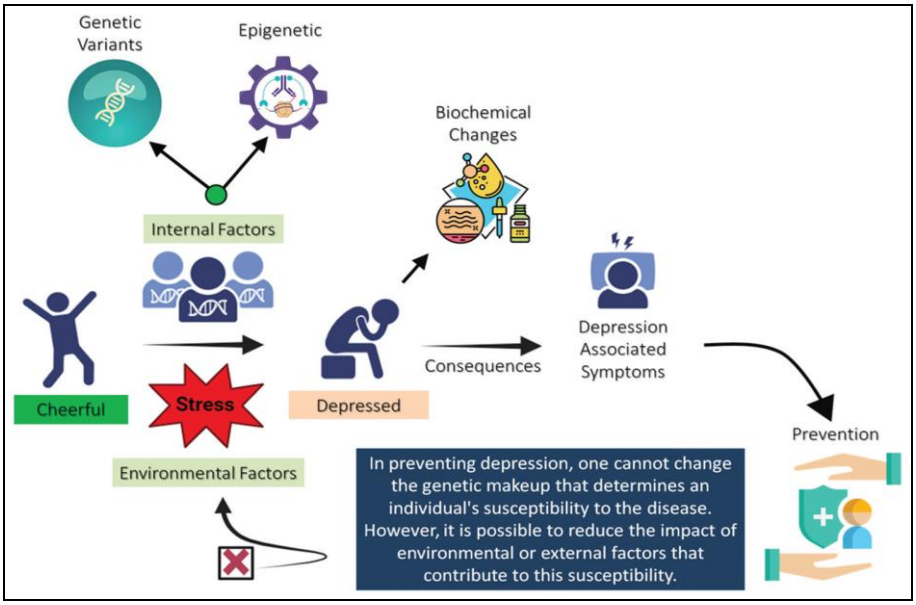

Fig 5: Flow diagram showing the causes and prevention of depression

1. Environmental Factors

- Long-term unemployment
- Financial difficulties
- Workplace stress
- Loneliness
- Abusive or unsupportive relationships
- Childhood physical or sexual abuse
- Bullying, peer pressure or social rejection
- Loss of a loved one
- Serious medical diagnosis (e.g., cancer, HIV)
- Synthetic chemicals
- Noise pollution
- Electrical pollution
- Natural and Catastrophic Disasters

2. Personal and Biological Factors

- Family history (genetic predisposition)
- Personality traits: low self-esteem, anxiety, perfectionism, negative thinking
- Chronic illnesses (e.g., cancer, HIV, Parkinson's disease, terminal illnesses)
- Drug and alcohol abuse or withdrawal
- Certain medical treatments and drugs (e.g., interferons, beta-blockers, contraceptives, antipsychotics, hormonal agents, anticonvulsants).
- Childhood difficulties

3. Genetic Factors

- Family History
- Heritability

4. Biochemical Factors

- Neurotransmitter Imbalances
- Hormonal Changes

5. Psychological Factors

- Cognitive Patterns
- Trauma History

Pathophysiology of Depression

Depression occurs due to disturbances in biological, psychological, and environmental factors. Several factors play an important role in the development of depression. These include imbalance of neurotransmitters in the brain, changes in brain plasticity (neuroplasticity), inflammation, genetic factors, and stress-related changes in the hypothalamic–pituitary–adrenal (HPA) axis. These factors together contribute to the development and progression of depression. These factors are explained in depth in the section that follows.

1. Genetic Influences

Genetic factors play an important role in the development of depression. Studies involving families, twins, and adopted individuals suggest that about 30–40% of the risk of developing depression is related to genetic factors. Research has also shown that first-degree relatives (such as parents, siblings, or children) of people with depression have a higher chance of developing the disorder compared to the general population. This indicates that depression can run in families and may be partly influenced by inherited genes.

However, genetics does not explain the entire risk. About 60–70% of the risk is related to environmental factors, including stress, traumatic experiences, and negative life events. The interaction between genes and environmental factors plays a key role in determining a person's vulnerability to depression. Identifying these interactions is difficult because depression involves many genes and environmental influences.

In addition to genetic and psychosocial factors, other biological and environmental factors may also contribute to the development and progression of depression [23].

2. Monoamine Hypothesis of Depression

One of the main explanations for the development of depression is the monoamine hypothesis. This theory suggests that depression occurs when there is a decrease in certain brain neurotransmitters, mainly serotonin (5-HT), norepinephrine (NE), and dopamine (DA).

This idea was developed from several important observations. First, doctors noticed that tuberculosis patients treated with the drug iproniazid showed improvement in mood. Second, the drug imipramine, which was originally developed as an antipsychotic, was later found to have antidepressant effects. Third, patients who were treated with the antihypertensive drug reserpine developed depressive symptoms, which could be improved with imipramine. These findings suggested that changes in brain chemicals are related to depression.

Initially, researchers believed that depression was mainly caused by low levels of norepinephrine and dopamine, known as the catecholamine hypothesis. Later, the importance of serotonin was discovered, which led to the broader monoamine theory of depression. This theory helped in the development of many antidepressant drugs that increase the levels of these neurotransmitters in the brain.

Several factors can cause the deficiency of monoamines in the brain. These include reduced synthesis of neurotransmitters, which may occur due to nutritional deficiencies or genetic factors affecting enzyme activity. Another cause may be increased breakdown of neurotransmitters by the enzyme monoamine oxidase (MAO). In addition, rapid reuptake of neurotransmitters by brain transporters can reduce their availability in the synaptic cleft. Changes in receptor function and signal transmission may also disturb neurotransmitter activity, contributing to depression [24, 25].

The monoamine hypothesis led to the development of the first generation of antidepressant drugs, such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). These drugs work by increasing the levels of monoamine neurotransmitters in the brain. MAOIs increase neurotransmitter levels by blocking the enzyme monoamine oxidase, which normally breaks down these chemicals. TCAs work by preventing the reuptake of neurotransmitters, allowing them to remain longer in the synaptic cleft.

However, these first-generation drugs often caused serious side effects because they also affected other receptors in the brain. To overcome this problem, second-generation antidepressants were developed. These include selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and dual serotonin and noradrenaline reuptake inhibitors.

Among these, SSRIs are commonly used as the first-line treatment for depression because they are safer and better tolerated. However, they may still cause some side effects such as nausea, insomnia, and sexual dysfunction.

Despite these treatments, not all patients respond to monoamine-based drugs, which suggests that other biological factors may also play a role in the development of depression [26].

3. Inflammation Hypothesis

The inflammation hypothesis suggests that inflammation plays an important role in the development of depression, especially in patients who do not respond well to traditional antidepressant treatments. Research has shown that people with depression often have increased levels of inflammatory cytokines such as TNF-α, IL-1, and IL-6. These inflammatory substances can reduce the levels of important neurotransmitters like serotonin, norepinephrine, and dopamine by increasing their reuptake and decreasing their synthesis. Inflammation can also break down tryptophan, the main precursor for serotonin, which further lowers serotonin levels in the brain. In addition, inflammatory cytokines may inhibit neurogenesis, the process of forming new neurons, which is important for brain function and mood regulation. Inflammation can also cause oxidative stress, leading to the production of harmful molecules that damage brain cells and disturb neurotransmitter balance. Furthermore, chronic inflammation has been linked to neurodegenerative diseases such as Alzheimer's and Parkinson's disease, which are also associated with depressive symptoms. Thus, inflammation and oxidative stress are considered important biological factors in the pathophysiology of depression [27].

Endocrine Hypothesis

The endocrine system plays an important role in depression. In many patients, the level of cortisol, which is known as the stress hormone, is increased. High cortisol levels can reduce the availability of tryptophan, a substance needed to produce serotonin (5-HT). As a result, serotonin levels decrease, which is linked to depression.

This increase in cortisol occurs due to problems in the hypothalamic–pituitary–adrenal (HPA) axis, which controls

the body's stress response. When the body experiences stress, the hypothalamus releases corticotropin-releasing hormone (CRH). This triggers the release of adrenocorticotropic hormone (ACTH) by the pituitary gland. The adrenal glands are then stimulated by ACTH to release cortisol.

Normally, cortisol sends a negative feedback signal to the hypothalamus and pituitary gland to stop further release of CRH and ACTH, helping maintain balance in the body. However, when this system becomes dysregulated, cortisol levels remain high and contribute to depression [23].

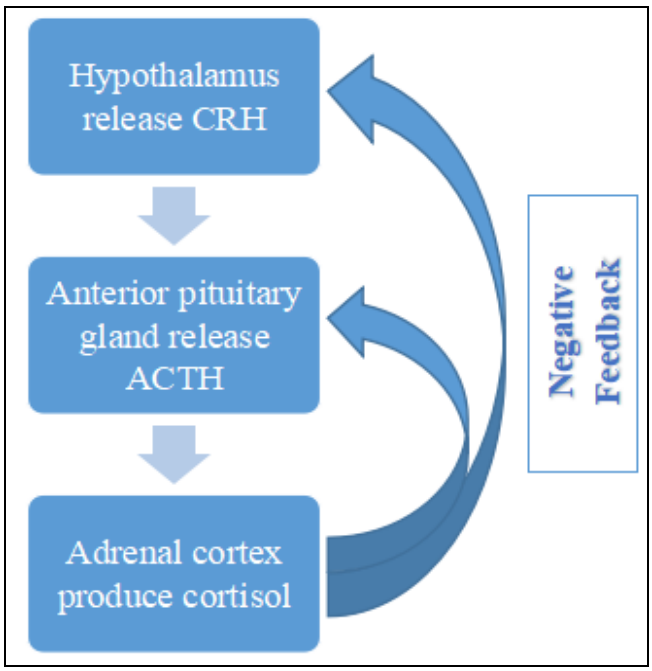

Fig 6: Schematic of the HPA axis [CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone].

Several factors can cause dysregulation of the HPA axis in depression. In many depressed individuals, the HPA axis becomes overactive, leading to increased release of CRH, ACTH, and cortisol, even when there is no stress. This results in long-term exposure to high cortisol levels. In addition, the negative feedback mechanism of the HPA axis may not work properly due to reduced sensitivity of glucocorticoid receptors, which causes continuous secretion of cortisol.

High cortisol levels can also reduce the production of brain-derived neurotrophic factor (BDNF). For nerve cells to proliferate and survive, BDNF is essential. When BDNF levels decrease, it may cause neurodegenerative changes, especially in brain areas like the hippocampus, which is involved in memory and emotions.

Hormonal imbalance related to the thyroid gland can also influence depression. Both hypothyroidism and hyperthyroidism may cause mood changes and depressive symptoms. Thyroid hormones regulate metabolism and brain function, and changes in their levels can affect neurotransmitters such as serotonin and norepinephrine, which are important for mood regulation. Treating thyroid problems, for example with triiodothyronine, may help improve depressive symptoms.

However, the relationship between hormones and depression is complex. Not all people with endocrine disorders develop depression, showing that hormonal imbalance is only one of several factors involved in depression [28, 29].

Glutamatergic and GABAergic Alterations

Depression is associated with changes in the balance between excitatory and inhibitory neurotransmitters in the brain. Glutamate, the main excitatory neurotransmitter, may become overactive in depression. Increased activity of NMDA receptors and reduced glutamate transporters can lead to higher levels of glutamate outside neurons, which may cause neuronal damage and contribute to depressive symptoms. These changes can also disturb synaptic plasticity, the brain's ability to adapt and form new connections.

On the other hand, GABA, the main inhibitory neurotransmitter, is often reduced in people with depression. Lower GABA levels, changes in GABA receptors, and dysfunction of GABAergic neurons reduce the brain's ability to control excessive neural activity involved in mood regulation.

Overall, an imbalance between glutamate (excitation) and GABA (inhibition) plays an important role in the development of depression. Targeting this neurotransmitter imbalance may help in developing new treatments for depression, although more research is still needed [30].

Neurotrophic Hypothesis

Recent studies show that people with depression may have reduced volume in certain brain areas, especially the hippocampus, which is important for memory and mood regulation. This reduction may occur due to stress, high glucocorticoid levels, glutamate toxicity, reduced neurotrophic factors, and decreased formation of new neurons.

The neurotrophic hypothesis suggests that depression is linked to reduced levels of brain-derived neurotrophic factor (BDNF). BDNF is a protein that supports the growth, survival, and function of neurons and helps maintain neuroplasticity, which is the brain's ability to form new connections.

Chronic stress can decrease BDNF levels, especially in brain regions like the hippocampus and prefrontal cortex, leading to impaired brain function and depressive symptoms. Genetic and epigenetic changes affecting the BDNF gene may also increase the risk of depression.

Antidepressant drugs such as SSRIs and tricyclic antidepressants can increase BDNF levels and improve neuroplasticity. Therefore, restoring BDNF signalling and neuronal growth may be an important strategy for treating depression [24, 31].

Circadian Rhythms Hypothesis

The circadian rhythms hypothesis suggests that depression may occur due to disturbances in the body's internal biological clock, which controls sleep–wake cycles and many body functions. When circadian rhythms are disrupted, it can affect mood regulation and increase the risk of depression.

People with insomnia or irregular sleep patterns may experience changes in neurotransmitters such as serotonin, making them more vulnerable to depression. Changes in circadian or clock genes, which control biological rhythms, may also contribute to depressive symptoms.

Depression can also disturb circadian rhythms, leading to sleep problems and worsening mood. For example, depressed individuals may show abnormal cortisol rhythms, such as reduced cortisol in the morning and higher levels in the evening.

Research shows that stabilizing circadian rhythms—by maintaining regular sleep schedules, getting sunlight exposure, and timing medication properly—can help improve depressive symptoms. Therefore, healthy sleep patterns are important in the prevention and treatment of depression [23, 32].

New Treatments for Depression [2]

1. Ketamine and Esketamine

Ketamine, an NMDA receptor antagonist, has been found to produce rapid antidepressant effects, even in patients with treatment-resistant depression. Esketamine, a nasal spray form of ketamine, has been approved by regulatory authorities for use in certain cases of treatment-resistant depression.

2. Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation is a non-invasive therapy that uses magnetic pulses to stimulate specific brain areas related to depression, particularly the dorsolateral prefrontal cortex. This method has been shown to reduce depressive symptoms and is generally considered safe and well tolerated.

3. Novel Pharmacological Approaches

Researchers are currently investigating new drug targets and mechanisms for treating depression. These include medications that act on the glutamatergic system, inflammatory pathways, and neurotrophic factors, with the aim of developing treatments that are faster-acting, more effective, and better tolerated than existing antidepressants.

4. Digital Therapeutics

Advances in digital health technologies have led to the development of digital therapeutics for depression. These include mobile applications, online therapy programs, and virtual reality-based interventions that provide psychotherapy, mindfulness training, and other supportive treatments remotely, helping to improve access to mental health care.

Brain parts involved in depression: [1]

Major depressive disorder (MDD) affects the structure, function, and chemical activity of different regions of the brain. These regions are mainly responsible for emotion control, memory, thinking ability, and decision making. Studies have shown that depression can cause changes in brain size, reduced activity, and loss of grey matter in some important brain areas.

According to the triune brain theory proposed by MacLean, the brain is divided into three main parts. The reptilian brain includes the brainstem and basal ganglia, which control basic functions like reflexes and routine movements. The limbic system, also called the mammalian brain, is responsible for emotions, survival behaviour, and reproduction. The neocortex, especially the prefrontal cortex, is involved in higher mental functions such as thinking, decision-making, and emotional regulation.

a. Prefrontal Cortex

The prefrontal cortex is responsible for thinking, planning, and controlling emotions. In people with depression, this region often shows reduced activity and blood flow. This can lead to poor decision-making, difficulty solving problems, and increased negative thinking, which may also increase suicidal tendencies.

b. Hippocampus

The hippocampus plays an important role in memory and learning. In depression, the size of the hippocampus becomes smaller. Studies show that its volume may decrease by 8–19%, and the left hippocampus is usually more affected than the right.

c. Amygdala

The amygdala is responsible for processing emotions such as fear, stress, and sadness. Changes in the size and activity of the amygdala have been observed in depression. These changes may also be related to early-life stress or trauma.

d. Raphe Nucleus

The raphe nucleus contains neurons that produce serotonin, a neurotransmitter that regulates mood. In depression, there is often a reduction in serotonin transporter levels, which indicates decreased serotonin activity in the brain.

e. Glial Cells

Glial cells support and protect neurons in the brain. Studies of people with depression have shown a decrease in glial cells in the prefrontal cortex and hippocampus, especially due to long-term stress.

f. Thalamus

The thalamus acts as a relay center that sends sensory information to different parts of the brain. It also helps regulate arousal, emotions, and memory. In depression, structural changes in the left thalamus have been observed, which may be related to the severity of depressive symptoms.

g. Striatum

The striatum, which is part of the basal ganglia, plays a key role in reward and motivation. In depressed individuals, studies show reduced activity in the striatum, which may explain the loss of interest and pleasure (anhedonia) commonly seen in depression.

h. Parietal Lobe

The parietal lobe is involved in planning, decision-making, and evaluating future outcomes. It is also part of the default mode network, which is associated with thinking and emotional processing. Changes in this region may contribute to the cognitive and emotional problems seen in depression.

Types of Depression [33]

Depression is a complex mental health disorder that presents in several forms. The major types of depression include Major Depressive Disorder, Bipolar Depression, Dysthymia or Persistent Depressive Disorder, Postpartum Depression, Melancholic Depression, Minor Depressive Disorder, and Seasonal Affective Disorder.

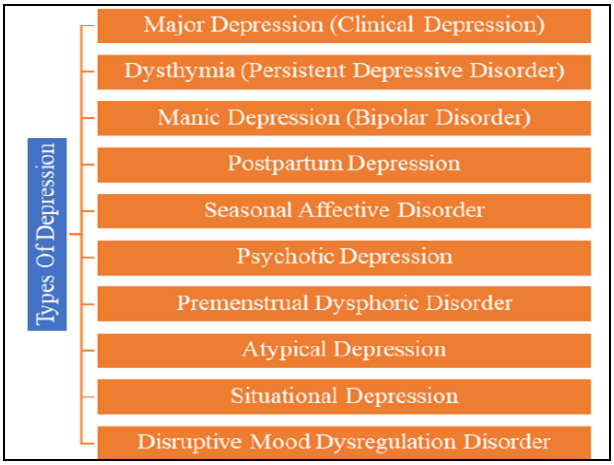

Fig 7: Types of Depressive Disorder

A. Major Depressive Disorder (MDD)
Major Depressive Disorder (MDD), commonly referred to as clinical depression, is one of the most prevalent and severe forms of depression. It is characterized by one or more episodes of intense depressive symptoms lasting for at least two weeks. These symptoms can significantly interfere with daily functioning, including the ability to work, sleep, study, eat, and participate in activities that were previously enjoyable. Individuals with MDD often experience persistent sadness or feelings of emptiness and hopelessness. Other common symptoms include loss of interest in pleasurable activities, feelings of guilt or worthlessness, changes in appetite or body weight, sleep disturbances such as insomnia or excessive sleeping, fatigue or reduced energy, difficulty concentrating or making decisions, and recurrent thoughts of death or suicide.

B. Dysthymia or Persistent Depressive Disorder (PDD)
Persistent Depressive Disorder (PDD), also known as dysthymia, is a chronic form of depression characterized by a continuously low mood lasting for at least two years in adults or one year in children and adolescents. Although the symptoms are generally less severe than those observed in Major Depressive Disorder, they are long-lasting and can significantly affect an individual's daily functioning, relationships, and overall quality of life.

C. Bipolar Disorder
Bipolar disorder, previously known as manic depression, is a mental health condition characterized by alternating episodes of depression and mania or hypomania. Individuals with bipolar disorder experience extreme mood changes that include emotional highs (mania) and lows (depression). Depressive episodes may present with symptoms similar to major depression, while manic episodes are characterized by elevated or irritable mood, impulsive behavior, racing thoughts, increased energy, grandiosity, and a decreased need for sleep. Bipolar depression is also often associated with hypersomnia and psychomotor retardation.

D. Postpartum Depression (PPD)
Postpartum Depression is a form of depression that occurs after childbirth. It is usually associated with hormonal changes, physical stress, and the emotional challenges of caring for a newborn. This condition typically develops within a few weeks to several months after delivery and can persist for up to a year if untreated.

E. Seasonal Affective Disorder (SAD)
Seasonal Affective Disorder (SAD) is a type of depression that typically occurs during specific seasons, most commonly in winter, due to reduced exposure to sunlight. Symptoms often improve during spring and summer. Treatment options for SAD include light therapy, antidepressant medications, and psychotherapy. Light therapy alone is effective in approximately half of the patients.

F. Psychotic Depression
Psychotic depression is a severe form of major depressive disorder in which depressive symptoms occur along with psychotic features such as delusions or hallucinations. Individuals may experience false beliefs, hear voices, or have distorted perceptions that are usually related to feelings of guilt, worthlessness, or illness. This condition requires immediate medical treatment as it is associated with a higher risk of suicide.

G. Premenstrual Dysphoric Disorder (PMDD)
Premenstrual Dysphoric Disorder is a severe form of premenstrual syndrome (PMS) characterized by emotional and physical symptoms that occur during the luteal phase of the menstrual cycle and usually improve after menstruation begins. Common symptoms include mood swings, irritability, depression, anxiety, fatigue, and difficulty concentrating.

H. Atypical Depression
Atypical depression is a subtype of major depressive disorder characterized by mood reactivity, meaning a person's mood may temporarily improve in response to positive events. Other common symptoms include increased appetite, weight gain, excessive sleeping (hypersomnia), fatigue, and heightened sensitivity to rejection.

I. Situational Depression
Situational depression, also known as adjustment disorder with depressed mood, occurs in response to a specific stressful life event or situation, such as loss of a loved one, divorce, financial problems, or major life changes. The depressive symptoms usually appear within a short time after the stressful event and may improve once the situation is resolved or coping strategies are developed.

J. Disruptive Mood Dysregulation Disorder (DMDD)
Disruptive Mood Dysregulation Disorder is a childhood mental health condition characterized by severe and recurrent temper outbursts that are disproportionate to the situation, along with a persistently irritable or angry mood between outbursts. The disorder typically begins before the age of 10 and can significantly affect social, academic, and family functioning.

K. Melancholic Depression
Melancholic depression is a severe subtype of depression that is more commonly observed in older adults and individuals with severe or psychotic depression. It is characterized by a profound loss of pleasure in almost all activities or a lack of response to pleasurable stimuli. Other features include worsening of depressive symptoms in the morning, early morning awakening, marked psychomotor retardation or agitation, significant loss of appetite or weight, and excessive or inappropriate feelings of guilt.

Treatment / Management of Depression [34]

Management of depression begins with a proper assessment and correct diagnosis. The doctor collects information through patient history, physical examination and mental status examination. Information from family members is also helpful to understand the patient's condition better.

Treatment for depression mainly includes medications and psychological therapies. Common treatment methods are antidepressant drugs, cognitive behavioral therapy (CBT), interpersonal therapy (IPT), electroconvulsive therapy (ECT) and psychosocial support.

In some patients where depression does not improve with usual treatment, other methods may be used. These include repetitive transcranial magnetic stimulation (rTMS), light therapy, transcranial direct current stimulation, vagus nerve stimulation, deep brain stimulation and sleep deprivation therapy.

Studies show that combining medicines with psychotherapy gives better results than using only one treatment method.

1. Antidepressant Medications: Selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and other classes of antidepressants are commonly prescribed to alleviate symptoms of depression. These medications work by increasing the availability of neurotransmitters such as serotonin and norepinephrine in the brain, helping to regulate mood.

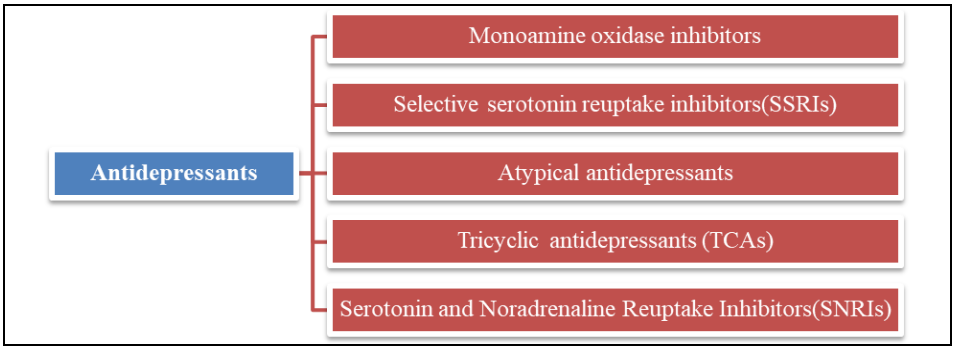

Fig 8: Classification of Antidepressant Medications

Reversible inhibitors of MAO-A (RIMAs): Monoamine oxidase inhibitors (MAOIs) work by blocking the monoamine oxidase enzyme, which breaks down neurotransmitters such as dopamine, norepinephrine, and serotonin. They were among the first antidepressant drugs discovered. However, due to their side effects and risk of drug interactions, MAOIs are usually not used as the first-line treatment for depression.

Drugs

- Moclobemide
- Clorgyline
- Isocarboxazid
- Phenelzine
- Selegiline
- Tranylcypromine

Administration

Isocarboxazid	• The starting dose is 20 mg daily, and the usual maintenance dose is 20 to 60 mg daily.
Phenelzine	• The starting dose is 45 mg daily, and the usual maintenance dose is 60 to 90 mg daily.

Fig 9: Administration of Monoamine Oxidase Inhibitors

Adverse effects

- Nausea
- Dizziness
- Headache
- Insomnia
- Rarely Excitement
- Liver Damage
- Potential for serotonin syndrome
- Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs): Selective serotonin reuptake inhibitors (SSRIs) are a group of drugs commonly used to treat depression. They are often considered the first-line treatment because they are safe, effective, and well tolerated. SSRIs are also used to treat several other mental health disorders and are approved for use in both adults and children.

Drugs

- Fluoxetine
- Sertraline
- Citalopram
- Escitalopram
- Dapoxitine
- Paroxetine
- Fluvoxamine

They are the most widely prescribed antidepressants.

Administration

Citalopram	• The starting dose is 20 mg daily, and the usual maintenance dose is 20 to 40 mg daily.
Escitalopram	• The starting dose is 5-10 mg daily, and the usual maintenance dose is 10 to 20 mg daily.

Fig 10: Administration of Selective Serotonin Reuptake Inhibitors

Adverse effects

- Sexual dysfunction
- Headache
- QTc prolongation
- Nausea
- Vomiting
- Loose Motions
- Dizziness
- Occasionally Insomnia

Atypical antidepressants: Atypical antidepressants are antidepressant drugs that work differently from most traditional antidepressants. Common antidepressants such as SSRIs, SNRIs, TCAs, and MAOIs mainly act by increasing the levels of monoamine neurotransmitters like serotonin and norepinephrine. In contrast, atypical antidepressants use different mechanisms of action to help relieve depressive symptoms.

Drugs
- Trazodone
- Mianserin
- Mirtazapine
- Bupropion
- Amoxapine
- Tianeptine
- Amineptine
- Netazodone

Administration

Bupropion	• The starting dose is 150 mg daily, and the usual maintenance dose is 300 mg daily.
Mirtazapine	• The starting dose is 15 mg daily, and the usual maintenance dose is 15 to 45 mg daily.

Fig 11: Administration of Atypical Antidepressants

Adverse effects Agomelatine- hepatotoxicity
- Mirtazapine-Sedation, Weight gain
- Bupropion- Seizures
- Trazodone - Arrhythmia
- Mianserin - blood dyscrasias, liver dysfunction

Tricyclic antidepressants (TCAs): Tricyclic antidepressants (TCAs) are a group of drugs used to treat major depressive disorder (MDD). They work by blocking the reuptake of neurotransmitters such as serotonin and norepinephrine, which helps regulate mood, attention, and pain. TCAs are usually considered second-line treatments, often used when selective serotonin reuptake inhibitors (SSRIs) are not effective. They are called "tricyclic" because their chemical structure contains three interconnected rings.

Drugs

a. NA+ 5HT reuptake inhibitors:
- Imipramine
- Amitriptyline
- Clomipramine
- Doxepin
- Dothiepin
- Nortriptyline

b. Predominantly NA reuptake inhibitors:
- Desipramine
- Nortriptyline
- reboxetine

Administration

Amitriptyline	• The starting dose is 50 mg daily, and the usual maintenance dose is 100 to 200 mg daily.
Nortriptyline	• The starting dose is 25 mg daily, and the usual maintenance dose is 50 to 150 mg daily.

Fig 12: Administration of Tricyclic Antidepressants

Adverse effects
- Dry mouth
- Urinary Retention
- Constipation
- QRS prolongation
- Seizures
- Orthostatic Hypotension

Serotonin and noradrenaline reuptake inhibitors (SNRIs): Serotonin–norepinephrine reuptake inhibitors (SNRIs) are a group of antidepressant drugs that block the reuptake of both serotonin and norepinephrine. By preventing their reabsorption in the synapse, SNRIs increase the levels of these neurotransmitters, which enhances the stimulation of postsynaptic receptors. However, different SNRIs vary in their affinity for serotonin and norepinephrine transporters.

Drugs
- Venlafaxine
- Duloxetine
- Desvenlafaxine
- Milnacipran
- Levomilnacipran

Administration

Venlafaxine	• The starting dose is 75 mg daily, and the usual maintenance dose is 225 to 375 mg daily.
Desvenlafaxine	• The starting dose is 25 to 50 mg daily; the usual maintenance dose is 50 mg daily.

Fig 13: Administration of Serotonin and Noradrenaline Reuptake Inhibitors

Adverse effects
- Hypertension
- Headache
- Diaphoresis
- Bone resorption [35]

Psychotherapy: Cognitive Behavioral Therapy (CBT)

Cognitive Behavioral Therapy (CBT) is a type of psychological treatment that helps people identify and change negative thoughts and behaviors that affect their feelings and actions. During stressful situations, many people develop negative thinking patterns that make it difficult to solve problems. CBT helps individuals develop more positive and balanced thinking, which improves their ability to manage stress and cope with challenges.

Research studies, including Cochrane reviews, have shown that CBT is effective in treating many mental, behavioral, and physical health problems. In Japan, the National Health Insurance (NHI) began covering CBT for mood disorders in 2010, and later extended coverage to other psychiatric conditions such as bulimia nervosa, obsessive-compulsive disorder (OCD), PTSD, panic disorder and social anxiety disorder.

Randomized controlled trials have also shown that CBT can help manage problems like antisocial behavior, drug abuse, gambling, obesity, smoking, and attention deficit hyperactivity disorder (ADHD).

Along with CBT, other psychotherapies such as interpersonal therapy (IPT) are also commonly used to treat depression. These therapies focus on changing negative thought patterns, improving coping skills, and strengthening interpersonal relationships, which helps reduce depressive symptoms and improve overall functioning.

Psychotherapy can help individuals to

- Adapt to a crisis or current life difficulties
- Recognize negative thoughts and behaviors and replace them with healthier, positive ones
- Understand relationships and experiences and build better interactions with others
- Develop effective coping and problem-solving skills
- Identify factors contributing to depression and change behaviors that worsen it
- Restore a sense of control and satisfaction in life and reduce symptoms like hopelessness and anger
- Set realistic and achievable life goals
- Learn healthier ways to manage and accept distress [36, 37]

Music Therapy in Depression

Music therapy is a non-drug treatment used to help people with depression. In this therapy, trained therapists use music such as listening, singing, or playing instruments to improve a person's mood and emotional health.

Research shows that music therapy can improve thinking ability, emotional expression, and self-confidence in people with depression. It also helps patients express their stress, anxiety, and feelings through music.

Music can change a person's emotions. Slow and pleasant music helps reduce negative feelings and creates a calm and relaxed mood.

Music therapy can also affect the body. Music stimulates the limbic system of the brain, which controls emotions. This can influence heart rate, blood pressure, and breathing. Because of this, music therapy can reduce depression symptoms and psychological stress [38, 39].

Brain Stimulation Therapy

Brain stimulation therapy may be considered when medications or psychotherapy do not effectively relieve symptoms of depression. Several types of brain stimulation therapies are now available, and some are approved by the FDA for treating depression.

Although these therapies are used less frequently than medication and psychotherapy, they can be helpful for individuals whose depression does not respond to other treatments. Brain stimulation therapies work by stimulating or inhibiting specific areas of the brain using electrical or magnetic signals. This stimulation can be delivered either directly through electrodes implanted in the brain or indirectly through electrodes placed on the scalp. In some methods, magnetic fields are applied to the head to generate electrical activity in the brain. Some brain stimulation therapies have strong scientific evidence supporting their effectiveness in treating depression.

The brain stimulation therapies with the largest bodies of evidence include:

- Electroconvulsive therapy
- Repetitive transcranial magnetic stimulation
- Vagus nerve stimulation
- Magnetic seizure therapy
- Deep brain stimulation

Electroconvulsive Therapy (ECT)

Electroconvulsive Therapy (ECT) is a medical treatment in which small electrical currents are passed through the brain to produce a controlled seizure. Although the exact mechanism of how ECT works is not completely understood, it is known to provide fast and effective relief from severe depression. It is mainly used in patients who do not respond well to other treatments such as medications or psychotherapy [40].

Herbal Agents

Medicinal plants have attracted significant attention from researchers for the development of antidepressant agents because they have been traditionally used to treat various diseases, including psychiatric disorders, and generally produce fewer side effects compared to synthetic drugs. Many patients find it difficult to tolerate the side effects of conventional antidepressants or may not respond adequately to them, which can lead to discontinuation of treatment.

Another important factor is the high cost of antidepressant medications and psychotherapy, which makes treatment less accessible for many people. As a result, there is increasing interest in herbal medicines as alternative therapies for depression. Currently, several medicinal plants are being studied to evaluate their potential antidepressant effects [41].

Future Perspectives

Future research on depression should focus on improving the understanding of its complex biological and psychological mechanisms. Advances in genetics, neuroimaging, and molecular biology may help identify specific biomarkers for early diagnosis and personalized treatment. The development of novel antidepressant therapies targeting alternative pathways, such as glutamate signaling and neuroinflammation, offers promising directions for more effective and faster-acting treatments. In addition, digital health technologies, including mobile mental health applications and telepsychiatry, may improve access to mental health care and enable continuous patient monitoring. Integrating pharmacological treatments with psychotherapy, lifestyle modification, and preventive strategies will likely enhance treatment outcomes. Furthermore, greater emphasis on personalized medicine may allow clinicians to tailor treatments based on an individual's genetic profile, clinical characteristics, and environmental factors. Continued multidisciplinary research and global mental health initiatives will be essential to reduce the burden of depression and improve long-term patient well-being.

Conclusion

Depression is a complex and multifactorial mental health disorder that significantly affects individuals, families, and societies worldwide. It involves the interaction of genetic, biological, psychological, and environmental factors that alter brain function and emotional regulation. Changes in neurotransmitters such as serotonin, norepinephrine, and dopamine, along with dysfunction in brain regions like the prefrontal cortex, hippocampus, and amygdala, play key roles in its pathophysiology. Various forms of depression, including major depressive disorder, persistent depressive disorder, and bipolar depression, present with diverse symptoms and severity levels. Effective management requires a comprehensive approach that combines pharmacological treatments, such as antidepressant medications, with psychological therapies and lifestyle interventions. Early diagnosis and appropriate treatment are essential to reduce disease burden and improve patient outcomes. Continued research into the biological mechanisms and therapeutic strategies of depression is crucial for developing more effective, personalized treatments and enhancing the overall quality of life for affected individuals.

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