



A Review of Depression

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ABSTRACT

Depression is a widespread and potentially serious mental illness that can occur in people of any age and in any geographic region. It is characterized by persistent low mood, apathy, and impaired cognitive and physical functioning. Depressive disorders are among the leading causes of disability worldwide, according to global health data, which indicates that they significantly increase the burden of disease and reduce quality of life. In this article, we will provide an overview of depression, its causes, symptoms, and treatment options. Key etiological factors are discussed, such as psychosocial effects, environmental stressors, neurochemical imbalances, and genetic predisposition. Symptoms can include low mood, fatigue, sleep disturbances, difficulty concentrating, and, in severe cases, thoughts of suicide. Other therapies, such as medication (antidepressant medications), psychotherapy (e.g., cognitive behavioral therapy), and lifestyle modification are also discussed.

Keywords: Depression, Mental health, Neurotransmitters, Antidepressants, Mood disorders.

INTRODUCTION

Depression is a major mental health disorder that affects the way a person feels, thinks, and acts. The World Health Organization defines depression as a common and serious mental health disorder that causes persistent sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration.¹ According to clinical definitions, depression also known as major depressive disorder is a mood disorder characterized by a persistent sense of melancholy or disinterest that lasts for at least two weeks, along with physical and cognitive symptoms that interfere with day-to-day functioning.² Depression has a complicated pathophysiology that includes changes in neurotransmitters like serotonin, dopamine, and norepinephrine as well as interactions between genetic, biological, environmental, and psychological factors.³ Due to its pervasive effects on people, families, and societies, depression is a significant public health concern. It greatly lowers quality of life, raises the risk of suicide, and exacerbates a number of comorbid conditions, including diabetes and cardiovascular disease.⁴ Depression also has a significant financial impact because of medical expenses and lost productivity.⁵

Depression is very common throughout the world. Depression is one of the most prevalent mental illnesses in the world, affecting an estimated 280 million people. Its prevalence varies by region, age group, and gender, with women being more affected than men.⁶ Depression rates are rising in India as a result of lifestyle changes, urbanization, and psychosocial stressors.⁷ Due to stigma, ignorance, and restricted access to healthcare services, many patients receive insufficient or no treatment at all despite the availability of pharmacological and

psychological treatments.⁸ As a result, there is an increasing need to investigate safer, more accessible, and more effective treatment options, such as plant based and alternative therapies.⁹ This review aims to give a thorough overview of depression, including its pathophysiology, causes, symptoms, and available treatments, with a focus on new therapeutic approaches and the possible use of medicinal plants in the treatment of depression.¹⁰

Types of depression: Primary (Endogenous/ Biological Depression), Secondary (Exogenous/ Reactive Depressions)

Primary depression:¹⁰

A primary mood disorder is a disorder in the gene, biochemistry or neurophysiology that is not life event induced; it is also termed an endogenous depressive episode. depression is due to thinning out of norepinephrine and dopamine in the brain. neurotransmitter dysfunction is seen in Primary depression:

Table 1: Types of Primary Depression

Type I	Serotonin Deficiency Depression	Low serotonin: causes of mood disturbances, sleep dysfunction and anxiety-like behavior
Type II	Norepinephrine Deficiency Depression	Low NE levels cause poor concentration, no energy, low motivation.
Type III	Dopamine Deficiency Depression	Reduction of dopamine causes anhedonia and reduced reward-processing.
Type IV	Mixed Monoamine Depression	Combined deficiency of 5-HT, NE and DA is involved in severe depressive episodes.
Type V	HPA Axis stress Related Depression	Chronic stress induces hypercortisolism, and neuronal atrophy.



Secondary depression:

Secondary (reactive) depression is induced by external events, underlying diseases or use of drugs, and is precipitated by: Psychological stress or trauma, Chronic disease (diabetes, hypothyroidism, neurological disease), Illicit drug use (alcohol, opioids), Long-term use of drugs such as corticosteroids, beta blockers, and reserpine. A "textbook" cause of secondary depression is long-term reserpine-dependent monoamine depletion. Treatment of the underlying cause often results in resolution of response.¹¹

Classification of depression:

Based on symptom patterns, duration, and underlying causes, depression can be categorized into multiple types. The following are some of the main types of depression.

Major depressive disorder:

The most prevalent and severe type of depression is major depressive disorder. It is typified by a persistent low mood that lasts for at least two weeks, fatigue, feelings of worthlessness, loss of interest or pleasure (anhedonia), and difficulty concentrating. MDD severely impairs day-to-day functioning and, if left untreated, may result in suicidal thoughts.¹²

Persistent depressive disorder:

Dysthymia, another name for persistent depressive disorder, is a chronic type of depression in which symptoms are milder than those of major depressive disorder (MDD) but persist for a longer period of time, usually two years or longer.¹³ People who suffer from dysthymia frequently have persistently depressed moods, low self-esteem, and decreased productivity.¹⁴

Bipolar depression:

Bipolar disorder, which alternates between periods of mania or hypomania and depression, includes bipolar depression. Although the depressive episodes in bipolar disorder are comparable to those in major depressive disorder (MDD), different treatment strategies are needed because of the possibility of inciting manic episodes.¹⁵ Proper diagnosis is crucial to avoid inappropriate therapy.¹⁶

Seasonal affective disorder:

Seasonal affective disorder is a kind of depression that manifests at particular times of the Year, usually in the winter when there is less exposure to sunlight. Low mood, insomnia, increased appetite, and weight gain are some of the symptoms.¹⁷ One popular and successful treatment is light therapy.¹⁸

Postpartum depression:

After giving birth, women experience postpartum depression, which is marked by extreme mood swings, anxiety, exhaustion, and trouble bonding with the newborn.¹⁹ Hormonal fluctuations, psychological adjustment, and social factors all have an impact. For the

mother and child to be healthy, early diagnosis and treatment are crucial.²⁰

Etiology:

Biological, psychological, and environmental factors interact to cause depression, which is a multifactorial disorder. Effective prevention and treatment plans require an understanding of these causes.

Biological factors:**Genetics:**

Depression is largely influenced by genetic predisposition. According to twin and family studies, the heritability of depression is thought to be between 30 and 40 percent, meaning that people with a family history of the condition are more vulnerable.²¹ There are several genes at play, each of which has a minor impact on the total susceptibility.²²

Neurotransmitter imbalance:

Depression is closely linked to imbalances in important neurotransmitters like serotonin, dopamine, and norepinephrine. While dopamine is linked to motivation and reward, norepinephrine is linked to alertness and stress response, and decreased serotonin levels are linked to mood disorders.²³ Many antidepressant treatments are based on dysregulation in these systems.²⁴

Psychological factors:**Stress:**

One of the main causes of depression is ongoing stress. Long-term stress can change the structure and function of the brain, especially the hypothalamic-pituitary-adrenal (HPA) axis, which can result in elevated cortisol levels and depressive symptoms.²⁵

Trauma:

Abuse, neglect, or the death of a loved one are examples of early life trauma that greatly increases a person's susceptibility to depression in later life. Long-term alterations in stress response systems and emotional regulation may result from such experiences.²⁶

Personality traits:

Neuroticism, low self-esteem, and pessimism are among the personality traits linked to an increased risk of depression. These characteristics affect how people view and react to stressful situations in their lives.²⁷

Environmental factors:**Life events:**

Depressive episodes can be brought on by significant life events like losing one's job, losing a loved one, getting divorced, or suffering from a serious illness. These incidents frequently serve as triggers, particularly for those who are already at risk.²⁸



Socioeconomic conditions:

Higher rates of depression are closely associated with low socioeconomic status, unemployment, inadequate education, and unstable finances. Chronic stress and limited access to healthcare are exacerbated by these conditions.²⁹

Family issues:

Depression risk factors include dysfunctional relationships, family disputes, and a lack of emotional support. Negative family dynamics can exacerbate pre-existing symptoms and impede healing.³⁰

Pathophysiology of depression:

Numerous biological systems, including immune responses, neurotransmitters, neuroendocrine pathways,

and structural alterations in the brain, are involved in the intricate pathophysiology of depression. To explain the underlying mechanisms, a number of theories have been put forth.

Monoamine hypothesis:

According to the monoamine hypothesis, the main cause of depression is a lack of monoamine neurotransmitters in the brain, specifically serotonin, dopamine, and norepinephrine. These neurotransmitters control emotional reactions, motivation, and mood. Depression symptoms are linked to a decrease in their levels or compromised signalling.³¹ The way that many antidepressants work, like selective serotonin reuptake inhibitors (SSRIs), which raise neurotransmitter availability, lends credence to this theory.³²

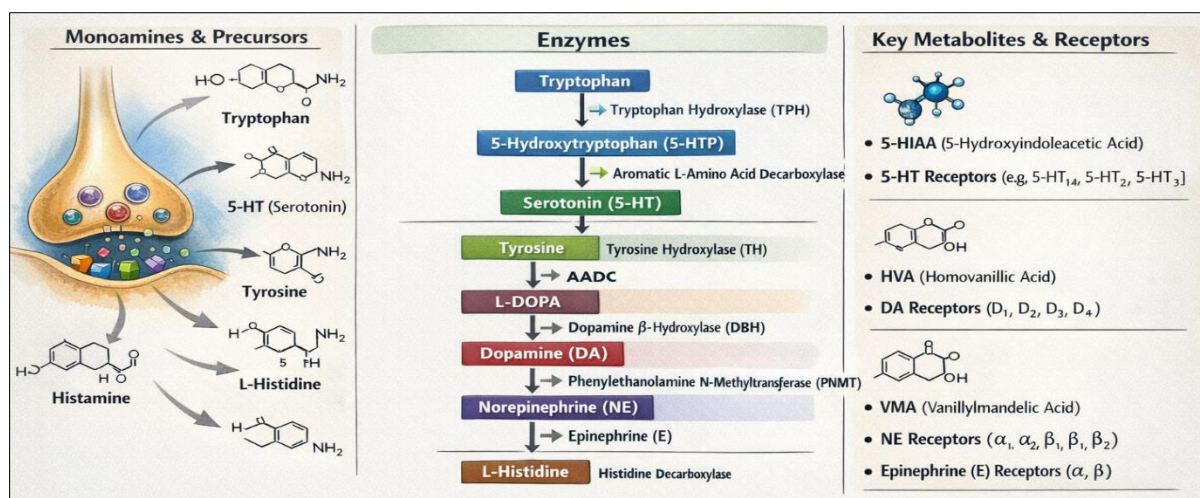


Figure 1: Monoamine Pathway

HPA axis dysfunction:

Another important component of depression is dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Prolonged stress causes the HPA axis to remain activated, which raises cortisol levels. This hormonal imbalance can lead to depression and have a detrimental impact on brain function, especially in areas related to mood regulation.³³

Neuroinflammation:

According to recent research, depression may be significantly influenced by inflammation. Depressed people have been found to have higher levels of pro-inflammatory cytokines like interleukins and tumor necrosis factor-alpha (TNF- α). By changing neurotransmitter metabolism, neuroendocrine function, and neural plasticity, these inflammatory mediators may exacerbate depressive symptoms.³⁴

Brain structure changes (hippocampus and amygdala):

Depression is linked to structural and functional alterations in particular brain regions. Patients with depression frequently exhibit decreased hippocampal volume, which may be brought on by long-term stress and high cortisol

levels. Increased activity in the amygdala, which is in charge of processing emotions, may result in more intense negative emotional reactions.³⁵

Signs and symptoms of depression:

Numerous symptoms of depression can impact one's emotional, physical, and cognitive abilities. Although the intensity and duration of these symptoms vary, they seriously hinder day-to-day functioning.

Emotional symptoms:

The most noticeable aspects of depression are emotional symptoms. People frequently feel depressed, hopeless, empty, and agitated. Another important trait is the loss of interest or enjoyment in once-pleasurable activities (anhedonia).³⁶ Additionally, patients may experience emotional numbness, excessive guilt, and worthlessness.³⁷

Physical symptoms:

Numerous somatic or physical symptoms are frequently linked to depression. These include persistent and exhaustion and decreased vitality, sleep disorders (hypersomnia or insomnia), and variations in body weight or appetite. Additionally, unexplained aches and pains that cannot be linked to other medical conditions may be

reported by patients.³⁸ The general quality of life may be further deteriorated by such symptoms.³⁹

Cognitive symptoms:

Another significant component of depression is cognitive impairment. People may have trouble focusing, make decisions, and think more slowly. Pessimism and self-criticism are prevalent negative thought patterns. In extreme situations, patients may experience suicidal thoughts or recurrent thoughts of death, which call for prompt medical attention.⁴⁰

Diagnosis of depression:

Standardized diagnostic criteria, validated screening tools, and clinical evaluation are the main factors used to diagnose depression. To effectively manage depression and distinguish it from other mental or physical disorders, an accurate diagnosis is crucial.

Clinical criteria (dsm-5):

The American Psychiatric Association's criteria are used to diagnose major depressive disorder. The DSM-5 states that a patient must have at least five symptoms that cause significant functional impairment and last for at least two weeks. These symptoms include depressed mood, loss of interest, fatigue, sleep disturbances, and feelings of worthlessness.⁴¹ These standards aid in improving clinical reliability and standardizing diagnosis.⁴²

Screening tools (phq-9, ham-d scale):

Depression is screened for and its severity evaluated using a number of standardized instruments. A popular self-report tool that assesses depression symptoms using DSM criteria is the Patient Health Questionnaire-9 (PHQ-9).⁴³ A clinician can use the Hamilton Depression Rating Scale (HAM-D) to measure the intensity of symptoms and track how well a treatment is working. Both clinical and research settings can benefit from these tools.⁴⁴

Differential diagnosis:

To differentiate depression from other mental illnesses like schizophrenia, bipolar disorder, anxiety disorders, and medical conditions like hypothyroidism or neurological disorders, differential diagnosis is essential. Appropriate treatment plans are ensured by proper assessment, which also helps prevent misdiagnosis.⁴⁵

Treatment of depression:

Both pharmaceutical and non-pharmacological methods are used in the treatment of depression. The severity of the patient's symptoms, medical history, and reaction to prior treatments all influence the treatment plan.

Pharmacological treatment:⁴⁶⁻⁴⁹

Non-pharmacological treatment:

Non-pharmacological methods are crucial for managing depression and are frequently used either by themselves in

mild cases or in conjunction with medication in severe cases.

Table 2: Pharmacological Treatment

Class	Mechanism of Action
Selective serotonin reuptake inhibitors (SSRIS)	Because of their effectiveness and good safety profile, SSRIs are the first-line treatment for depression. By preventing serotonin from being reabsorbed into presynaptic neurons, medications like fluoxetine raise serotonin levels.
Serotonin-norepinephrine reuptake inhibitors (SNRIS)	By preventing serotonin and norepinephrine from being reabsorbed, SNRIs like venlafaxine and duloxetine improve mood and vitality.
Tricyclic antidepressants (TCAS)	TCAs are older antidepressants that prevent serotonin and norepinephrine from being reabsorbed, but they have more adverse effects including cardiotoxicity and anticholinergic effects.
Monoamine oxidase, (MAO) inhibitors	MAO inhibitors increase the availability of monoamine neurotransmitters by preventing their breakdown. Despite their effectiveness, their use is restricted because of possible drug interactions and dietary restrictions.

Psychotherapy (CBT, counseling):

Depression is frequently treated with psychotherapy, especially cognitive behavioral therapy (CBT). Its goal is to improve emotional well-being by recognizing and changing harmful thought patterns and behaviors.⁵⁰

Electroconvulsive therapy (ECT):

For severe or treatment-resistant depression, electroconvulsive therapy works well. It has demonstrated a quick improvement in symptoms and entails the induction of controlled seizures under anesthesia.⁵¹

Lifestyle modifications (exercise, diet, sleep):

A balanced diet, regular exercise, and enough sleep are examples of lifestyle interventions that are essential for managing depression. Exercise has been demonstrated to improve mood by raising endorphin levels, and healthy eating and sleep promote mental wellness in general.⁵²⁻⁵³

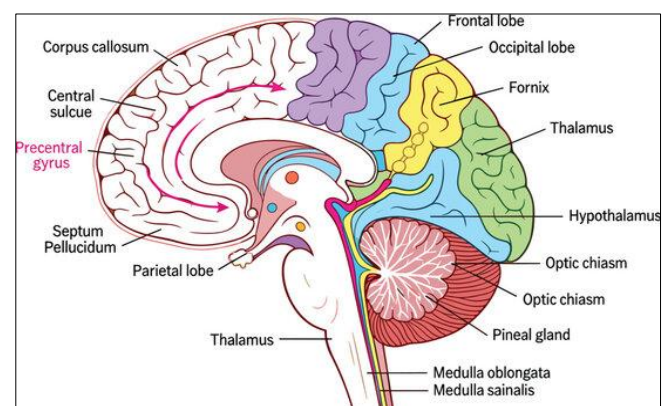


Figure 2: Brain regions

Herbal therapies for depression:

Herbal remedies are being investigated more and more as complementary and alternative therapies for depression. Compared to traditional antidepressants, they typically have fewer side effects and offer potential benefits. An overview of significant herbal remedies is provided below.

Perforate st. john's wort:

Most extensively researched herbal remedy for depression. includes hyperforin and hypericin, which alter norepinephrine, dopamine, and serotonin. shown in some studies to be comparable to conventional antidepressants and effective for mild to moderate depression.⁵⁴

Saffron:

Safranal and crocin are the active ingredients. increased serotonin levels and antioxidant effects, demonstrating antidepressant activity. Clinical trials demonstrate a decrease in depressive symptoms and an improvement in mood.⁵⁵

Ginkgo biloba:

acts as an antioxidant and enhances cerebral blood flow. Helps to stabilize mood by modifying monoaminergic neurotransmission. May alleviate depression related cognitive symptoms.⁵⁶

Ashwagandha:

An adaptogenic herb that lowers cortisol and stress. uses GABAergic and serotonergic modulation to show anxiolytic and antidepressant effects.⁵⁷

Turmeric:

Curcumin is the active ingredient. Antioxidant and anti-inflammatory qualities aid in lowering neuroinflammation associated with depression. Demonstrated in clinical trials to alleviate depression symptoms and elevate mood.⁵⁸

Bacopa monnieri:

Improves cognitive performance and lessens depression brought on by anxiety. Serotonin, dopamine, and antioxidant activity are all modulated by this mechanism.⁵⁹

Lavender:

Essential oil that is taken orally or used in aromatherapy. demonstrates mild antidepressant and anxiolytic effects by modulating GABA.⁶⁰

Rhodiola rosea:

Adaptogenic herb that lessens depressive symptoms brought on by stress and exhaustion. affects the regulation of the HPA axis and monoamine neurotransmitters.⁶¹

Passion flower:

This is used historically to treat anxiety and sleep issues. demonstrates antidepressant effects through the serotonergic and GABAergic systems.⁶²

Chamomile:

A mild anxiolytic and sedative effects. helps people with mild depression symptoms feel less stressed and happier.⁶³

Complications of depression:

Untreated depression can have major negative effects on one's physical and mental well-being. These issues may raise the risk of death and drastically lower quality of life.

Suicide risk:

An elevated risk of suicide is one of the most serious consequences of depression. Suicidal thoughts or attempts may result from the enduring feelings of hopelessness, worthlessness, and despair that people with depression frequently experience. Research shows that underlying depressive disorders are linked to a significant percentage of suicide cases.⁶⁴ To avoid deadly consequences, early detection and intervention are essential.⁶⁵

Substance abuse:

Substance abuse, including alcohol and drug dependence, is often linked to depression. Substance abuse may be used by people as a coping strategy to ease emotional distress, which can exacerbate depressive symptoms and create a vicious cycle of addiction and declining mental health.⁶⁶ Treatment is more difficult and recovery rates are lower when co-occurring substance use disorders are present.⁶⁷

Chronic illness worsening:

Diabetes, heart disease, cancer, and other chronic illnesses can all be adversely affected by depression. It may worsen overall health outcomes by decreasing treatment adherence, compromising immune function, and raising the risk of complications.⁶⁸

Prevention of depression:

Reducing risk factors, fostering mental health, and putting early interventions into practice are the main goals of depression prevention. The prevalence and burden of depressive disorders can be considerably reduced by effective preventive measures.

Stress management:

Depression can be avoided by using effective stress-reduction methods like mindfulness, relaxation training, and coping mechanisms. One significant risk factor is chronic stress, which can be effectively managed to preserve resilience and emotional equilibrium.⁶⁹

Early diagnosis:

Early detection of depression symptoms lessens the severity and duration of the condition and enables prompt intervention. Early diagnosis and better results depend on screening programs in primary care and community settings.⁷⁰



Awareness programs:

Programs for mental health education and public awareness help lessen the stigma attached to depression and motivate people to get treatment. Better comprehension, early detection, and easier access to treatment result from increased awareness.⁷¹

Healthy lifestyle:

Depression can be avoided by leading a healthy lifestyle that includes regular exercise, a balanced diet, enough sleep, and abstaining from substance abuse. These elements support general physical and mental health.⁷²⁻⁷³

Future perspectives:

Research And Technological developments are creating new opportunities for the comprehension and treatment of depression. Innovative drug development, individualized treatment plans, And the incorporation of digital technologies are the main focuses of future strategies.

New drug development:

An important area of research is the creation of new antidepressants that target pathways other than monoamines. N-methyl-D-aspartate (NMDA) receptor antagonists, like ketamine, which exhibit quick antidepressant effects, are the subject of recent research on glutamatergic modulation.⁷⁴ New therapeutic targets are also being found thanks to research on neurotrophic factors and inflammatory pathways.⁷⁵

Personalized medicine:

The goal of precision or personalized medicine is to customize care according to a patient's clinical profile, biomarkers, and genetic composition. Pharmacogenomics is essential for anticipating drug response and reducing side effects, which enhances depression treatment results.⁷⁶ By choosing the best intervention for each patient, this method increases the efficacy of therapy.⁷⁷

Role of digital therapy and ai:

Mental healthcare is being revolutionized by digital health technologies, such as mobile applications, online cognitive behavioral therapy (CBT), and tools based on artificial intelligence (AI).

These tools facilitate real-time monitoring, increase accessibility, and offer patients with depression individualized interventions.⁷⁸ Additionally, early diagnosis and treatment outcome prediction are aided by AI-driven models.

DISCUSSION

Depression is a multifactorial disorder with intricate interactions between biological, psychological, and environmental factors, according to the discussion of numerous studies. The implications of these findings and their applicability to treatment approaches are covered in this section.

Biological insights:

Neurotransmitter systems other than the conventional monoamines are important, according to recent research. For instance, the pathophysiology of depression has been linked to dysregulation of the glutamatergic and GABAergic systems, providing new targets for therapeutic interventions.⁷⁹ The prefrontal cortex, hippocampus, and amygdala exhibit structural and functional abnormalities that are correlated with the severity of symptoms and cognitive deficits, according to neuroimaging studies.⁸⁰⁻⁸¹

Psychological and environmental factors:

Depression is still strongly predicted by psychological stress and early life trauma. According to longitudinal research, long-term stress changes neuroendocrine function and makes people more susceptible to depressive episodes in the future.⁸² The risk and progression of depression are greatly influenced by environmental factors like socioeconomic status and social support, underscoring the necessity of comprehensive treatment strategies.⁸³⁻⁸⁴

Treatment implications:

Treatment-resistant depression is still a significant problem despite the well-established effectiveness of pharmaceutical treatments, especially SSRIs and SNRIs. In refractory cases, new treatments like NMDA receptor antagonists, anti-inflammatory drugs, and neurostimulation methods show encouraging outcomes⁸⁵⁻⁸⁶. CBT and lifestyle changes are examples of non-pharmacological interventions that improve treatment results and reduce relapse.⁸⁷

Future directions:

Diagnosis, treatment choice, and adherence are likely to improve with the integration of digital therapies, AI-assisted monitoring, and personalized medicine. According to studies, AI models can identify patients who are at risk of relapse and predict how each patient will react to treatment, providing a more accurate and proactive method of managing depression.⁸⁸

CONCLUSION

Depression is a multifaceted, intricate mental illness that has serious emotional, cognitive, and physical repercussions. This review highlights the critical interplay of biological, psychological, and environmental factors in its etiology and pathophysiology, emphasizing the role of neurotransmitter dysregulation, neuroinflammation, HPA axis dysfunction, and structural brain changes. To lessen the intensity of depressive episodes, avoid consequences like substance abuse and suicide, and enhance general quality of life, early diagnosis and prompt intervention are crucial. Comprehensive management strategies are provided by non-pharmacological methods like psychotherapy, lifestyle changes, and digital interventions in addition to pharmacological treatments like SSRIs, SNRIs, and novel agents. Additionally, the incidence of depression can be considerably decreased by prevention techniques like stress



management, public awareness campaigns, and adopting healthy lifestyle.

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