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Depression Unraveled: Pathophysiology and Treatment Advances

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Abstract: Depression is a complicated, long-lasting, and recurrent mental illness that has a major impact on emotional, cognitive, and physical functioning and has a huge negative impact on global health. The World Health Organization (WHO) estimates that over 280 million people worldwide suffer from depression, making it a substantial contributor to the global illness burden and a primary cause of disability. In addition to lowering quality of life, the disorder raises the risk of morbidity and mortality, especially from suicide and related illnesses including diabetes and cardiovascular disease. Depression has a complex etiology that includes genetic, neurological, psychological, and environmental factors. Additionally, there is growing evidence that oxidative stress and inflammatory cytokines have a role in the neuroprogression of depression. An integrative approach that combines medication, psychotherapy, and lifestyle changes is used to treat depression. The first-line pharmaceutical treatments are still antidepressants such selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants. Psychotherapeutic approaches including interpersonal therapy (IPT) and cognitive-behavioral therapy (CBT) have also demonstrated notable effectiveness in enhancing results. Electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and ketamine-based therapies are being used more frequently for treatment-resistant cases. The potential of probiotics, anti-inflammatory drugs, and nutraceuticals as supplemental therapies has also been emphasized by recent studies. An extensive grasp of depression, including its epidemiology, symptomatology, etiology, neurobiological underpinnings, diagnostic techniques, and treatment developments, is the goal of this review. It highlights the significance of early detection, individualized treatment, and holistic care in effectively managing depression by combining recent research.

Keywords: *Pathophysiology, Depression, Pharmacotherapy, Psychotherapy, Neurobiology, Neurotransmitters, and the HPA Axis.*

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I. INTRODUCTION

A common mental illness, major depressive disorder or MDD affects mood, behavior, thought processes and physiological functions like eating and sleeping (1). Depression adds considerably two years lived with disability and the global burden of illness and it has a major socioeconomic impact due to lower productivity and increased healthcare spending (2). Pharmacists play a crucial role in medication management, screening, relapse prevention counseling, and adherence assistance (3). A persistent feeling of sadness and apathy is a hallmark of depression, a mood disorder (4,5). Rather than being the result of a single episode, depression is usually the result of a confluence of factors. Depression is not caused by just having too much or too little of a certain brain chemical. Other possible causes of depression include genetic susceptibility, stressful life events, and the brain's incapacity to control mood. Untreated mental health conditions can have a negative impact on the local economy, employment, safety, homelessness, and poverty. They could disrupt families and communities, impede children's and youth's academic advancement, and have an impact on the productivity of local businesses and health care costs. Misconceptions prevent about 60% of depressed people from seeking medical help. Many people believe that the stigma attached to mental health illnesses is undesirable in society and that it interferes with both one's personal and professional life. Even while there is compelling evidence

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that most antidepressants work, each patient may respond to medication in a unique way.

In ten more years, depression would be the second most prevalent disorder globally in terms of morbidity, according to WHO estimates. Nowadays, depression affects 1 in 5 women and 12 men. In addition to adults, 2% of schoolchildren and 5% of teenagers suffer from depression; most of these cases go undetected. The Great Depression has Despite the widespread perception that sadness is the primary cause of all psychiatric problems, this has been the most common reason for seeing a psychiatrist (6,7). The majority of patients display the myth surrounding depression. People still believe that drugs are merely lifelong sedatives, that it is caused by a personality deficit, or that it can be cured on one's own. All of these myths were created primarily for personal benefit by religious healers, inexperienced counselors, non-medical specialists, and a community that was ignorant of them. A better knowledge of and approach to psychiatrists has been the main factor contributing to the increase in patients, not necessarily an increase in prevalence. Thanks to better facilities and more recent drugs, depression is now easier to treat, and the majorities of patients recovers rapidly and return to their optimal functioning (8).

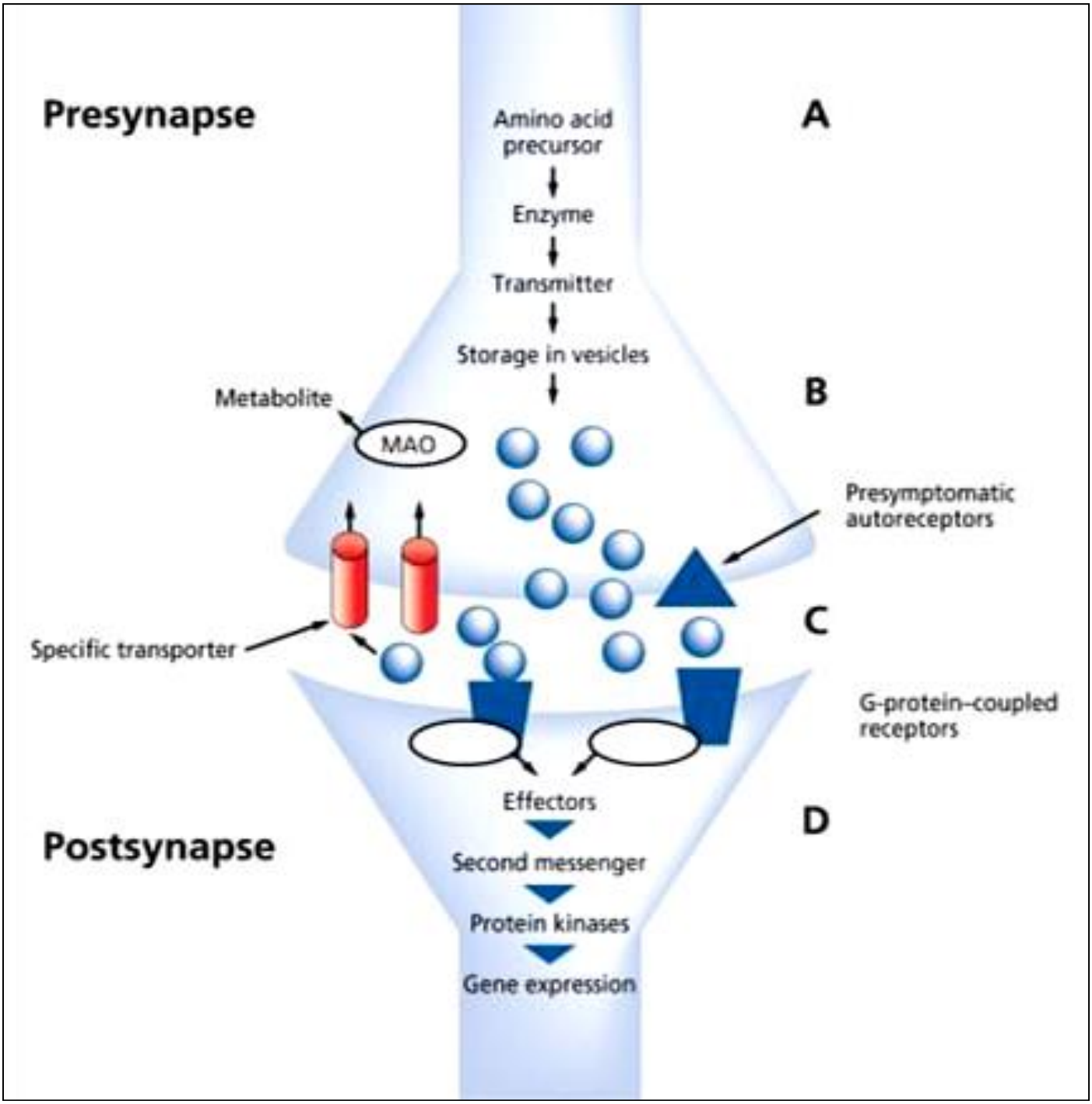

Fig 1 Mechanism of Synaptic Transmission

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II. SYMPTOMS OF DEPRESSION

Depression is a complex mental condition that can appear with a range of emotional, cognitive, behavioral, and physical symptoms. It is a long-term state of psychological and physiological changes that considerably lowers a person's quality of life rather than a transient depressive episode. To be diagnosed with major depressive disorder, a patient must exhibit at least five symptoms over a two-week period, at least one of which must be a low mood or a loss of interest or pleasure, according to the DSM-5 (9). The symptoms of depression are explained in depth in the section that follows.

- *Depressed Mood:*

A persistently down mood is the most common and basic sign of depression. Patients frequently report feeling gloomy, empty, or hopeless almost every day and for most of the day (10). Unlike fleeting melancholy, this mood state is persistent, disproportionate to life events, and often unaffected by good experiences. People may also describe feeling emotionally detached from their surroundings or emotionally numb under extreme circumstances (11).

- *Anhedonia:*

Anhedonia is considered the second cardinal sign of depression. It characterizes a markedly diminished degree of enjoyment or interest in almost all activities, including everyday tasks, social interactions, and pastimes (12,13). This symptom is crucial because it distinguishes depression from normal sadness or grief. Anhedonia may be associated with dopaminergic reward system dysfunction, namely in the mesolimbic system, according to neurobiological study (14).

- *Appetite and Weight Disturbances:*

Depression is often associated with significant changes in body weight and hunger. While some patients gain weight due to increased desire and appetites for meals heavy in carbs, others lose weight due to decreased appetite (15). These issues cannot be explained by deliberate dieting. Meta-analyses confirm a reciprocal relationship between depression and obesity and show the biological and psychological overlap between the two conditions (16).

- *Sleep Disturbances:*

Depression is often associated with changes in sleep patterns. Melancholic depression is closely associated with sleeplessness, particularly early morning awakening (terminal insomnia) (17). On the other hand, hypersomnia, or excessive sleep, is more prevalent in atypical depression, especially in young adults and adolescents (18). Studies on sleep architecture show that depressed patients have shorter rapid eye movement (REM) latency and less slow-wave sleep, which suggests neurobiological disruption of circadian rhythms (19).

- *Psychomotor Changes:*

Psychomotor symptoms include either psychomotor retardation (slowed speech, movement, and mental processes) or psychomotor agitation (restlessness, pacing, hand wringing) (20). Since both family members and medical professionals can observe these traits, they are objective markers of depression. Psychomotor slowdown is especially associated with sorrow and severe depressive episodes, whereas agitation is more common in anxious sadness (21).

- *Fatigue and Loss of Energy:*

The majority of people who suffer from depression say they feel exhausted and have decreased energy. Unlike normal fatigue, this symptom does not go away with rest or sleep (22). Fatigue reduces motivation and has a detrimental effect on social and professional functioning. Neuroendocrine research suggests that altered hypothalamic-pituitary-adrenal (HPA) axis activity may be the source of this symptom (23).

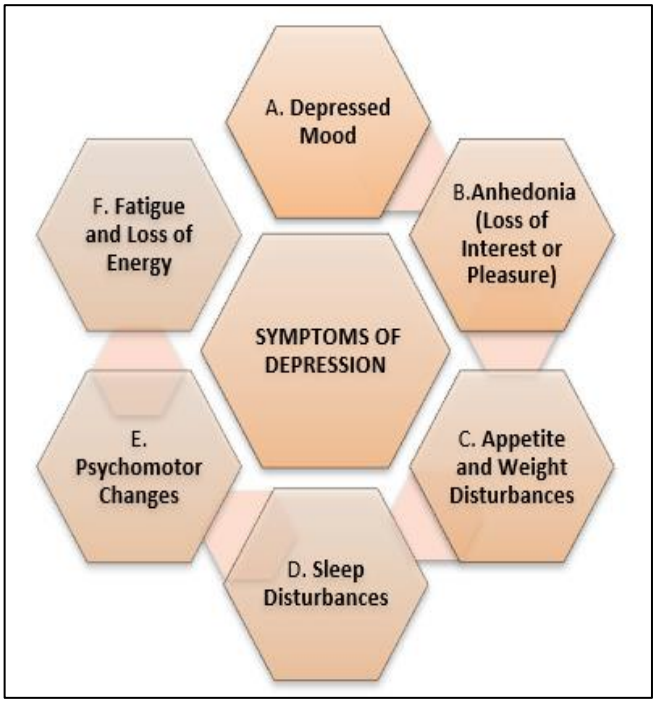

Fig 2 Symptoms of Depression

III. CAUSES AND RISK FACTORS OF DEPRESSION

Depression is a complex disorder that is influenced by a number of biological, psychological, and social factors. The best explanation for its genesis is a biopsychosocial model, in which the clinical condition is caused by a combination of neurobiological dysfunctions, environmental stressors, and hereditary predisposition (24).

- *Genetic Factors:*

There is a strong hereditary component to depression, according to research on adoption, twins, and families. First-degree relatives of individuals with depression are two to three times more likely to suffer from depression themselves than the general population (25). Major depressive disorder has 40% heritability, according to twin studies, highlighting the significant role of genetic factors (26). Genome-wide association studies (GWAS) have identified several

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susceptibility loci, particularly those related to stress-response pathways and neurotransmitter regulation (27).

➢ *Neurobiological Factors:*

One of the most widely accepted neurobiological theories of depression is the monoamine hypothesis, which postulates that reduced serotonin, norepinephrine, and dopamine synaptic availability contributes to depression (28). However, more recent research also connects the pathophysiology to GABAergic and glutamatergic problems (29). The hypothalamic-pituitary-adrenal (HPA) axis is often dysregulated in depressive individuals, leading to persistently elevated cortisol levels, according to neuroendocrine research (30). Neuroimaging results reveal both anatomical and functional changes in brain regions linked to mood regulation, such as the prefrontal cortex, hippocampus, and amygdale (31).

➢ *Psychological and Cognitive Factors:*

The core causes of depression, according to cognitive theories, include poor coping mechanisms, dysfunctional beliefs, and negative thought patterns (32). Beck's cognitive triad describes the tendency of depressed individuals to hold negative views about the environment, themselves, and the future (33). The learned helplessness theory states that persistent exposure to uncontrollable stress leads to sad conduct and hopelessness (34).

➢ *Environmental and Social Factors:*

Adverse life events, such as abuse, a loved one's death, childhood trauma, or persistent interpersonal conflict, are powerful triggers for depression (35). Socioeconomic disadvantages like poverty, unemployment, and low educational attainment significantly enhance the risk of experiencing depressive episodes (36). Social isolation and a lack of support raise the risk of depression even more, even if protective social networks might serve as a buffer (37).

➢ *Medical and Physiological Conditions:*

Depression frequently co-occurs with long-term illnesses such diabetes, heart disease, cancer, and chronic pain syndromes (38). These comorbidities significantly increase the burden and cost of healthcare in addition to deteriorating disease outcomes (39). Many medications, including corticosteroids, interferons, and some antihypertensives, have been documented to cause depressive symptoms as a side effect (40). Thyroid problems, perimenopause, and hormonal irregularities during postpartum periods can also cause depressive episodes (41).

➢ *Personality and Temperament:*

People with personality traits such high neuroticism, low self-esteem, and excessive dependency are more likely to experience depression (42). Personality disorders, especially avoidant and borderline personality disorders frequently co-occur with depression (43). These vulnerabilities and pressures interact to cause recurrent episodes.

➢ *Substance Use:*

Alcohol abuse, nicotine addiction, and illicit drug use significantly raise the risk of depression (44).

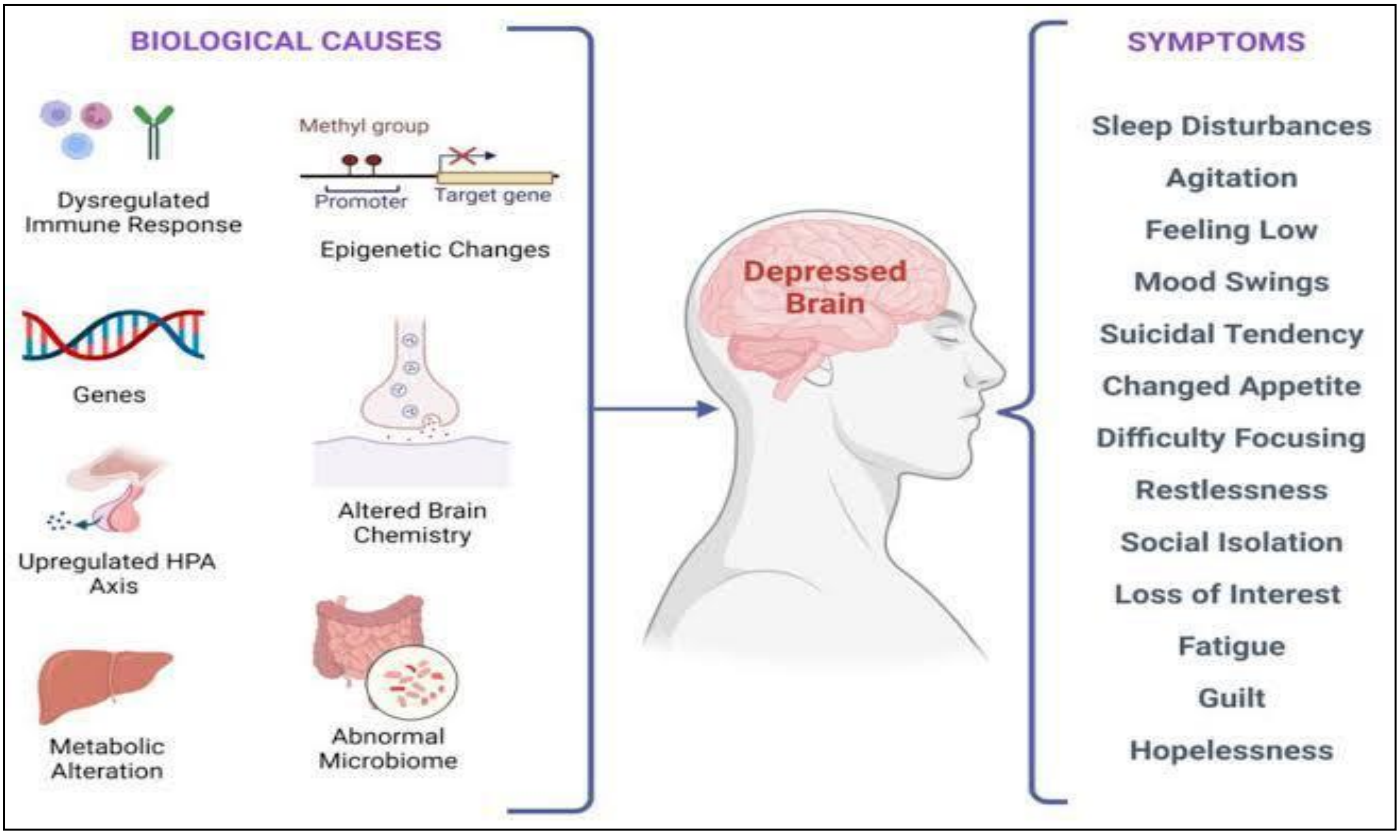

Fig 3 Causes and Risk Factors of Depression

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IV. CLASSIFICATION OF DEPRESSIVE DISORDER

Mood irregularities that affect emotional, cognitive and physical functioning are the hallmark of a group of mental illnesses called depressive disorders (45). These conditions are classified into several subgroups by the Diagnostic and Statistical Manual of Mental Diseases, Fifth Edition (DSM-5) and the International Classification of Diseases, 11th Revision (ICD-11) based on variables such as severity, duration, and associated traits (46).

- *Major Depressive Disorder (MDD):*

A diagnosis of Major Depressive Disorder, the most common and clinically significant form of depression, requires the presence of at least five depressive symptoms for at least two weeks. These symptoms include persistent sadness, anhedonia (loss of interest or pleasure), and fatigue, sleep disturbances, changes in appetite, and feelings of worthlessness, poor concentration, and recurrent thoughts of death. MDD severely hinders social, professional, and personal functioning and might present as a single episode or as recurrent episodes throughout a person's life.

- *Persistent Depressive Disorder (Dysthymia):*

Persistent depressive disorder, also known as dysthymia, is a chronic kind of depression with milder symptoms than major depressive disorder (MDD) that lasts for at least two years in adults (or a year in children and adolescents) (47). Though they are more chronic than intermittent, symptoms of dysthymia may include low self-esteem, poor appetite or overeating, sleep problems, tiredness, and depression.

- *Disruptive Mood Dysregulation Disorder (DMDD):*

The characteristic of DMDD, a childhood-onset depressive illness, is extremely frequent verbal or behavioral outbursts that are wildly out of proportion to the situation and incongruous with developmental stage. The child has been agitated or upset for the most of the day, nearly every day, between outbursts, for at least 12 months. This diagnosis helps differentiate youngsters with persistent irritability from those with pediatric bipolar disorder.

- *Premenstrual Dysphoric Disorder (PMDD):*

PMDD, a severe form of premenstrual syndrome, causes mood swings, irritability, depression, anxiety, and physical symptoms such headaches, breast tenderness, and bloating during the luteal phase of the menstrual cycle (48). The symptoms, which disappear a few days after the onset of menstruation, significantly impede daily functioning, interpersonal relationships, and job performance.

- *Depressive Disorder Due to Another Medical Condition:*

This disorder is characterized when depression symptoms are directly caused by the pathophysiological effects of a medical condition, such as hypothyroidism, Parkinson's disease, stroke, or Cushing's syndrome. The mood disorder is not better explained by another mental illness and causes a clinically significant impairment in functioning.

- *Substance/Medication-Induced Depressive Disorder:*

This type of depression happens during or soon after drug exposure, withdrawal, or substance addiction (48). Alcohol, sedatives, corticosteroids, and certain antihypertensive drugs are known to cause depressive states. Symptoms usually disappear after the medication is withdrawn or the treatment is discontinued.

- *Other Specified Depressive Disorder:*

This category is used when depressed symptoms cause significant pain and disability but do not fully meet the diagnostic criteria for any specific depressive disease. Examples include brief episodes of depression lasting four to thirteen days or depressive episodes without sufficient symptoms to be categorized as major depressive disorder.

- *Unspecified Depressive Disorder:*

The phrase "unspecified depressive disorder" is used when depression symptoms are present but insufficient information is available to provide a more accurate diagnosis. This is often used in emergency situations when a full diagnostic evaluation is not feasible.

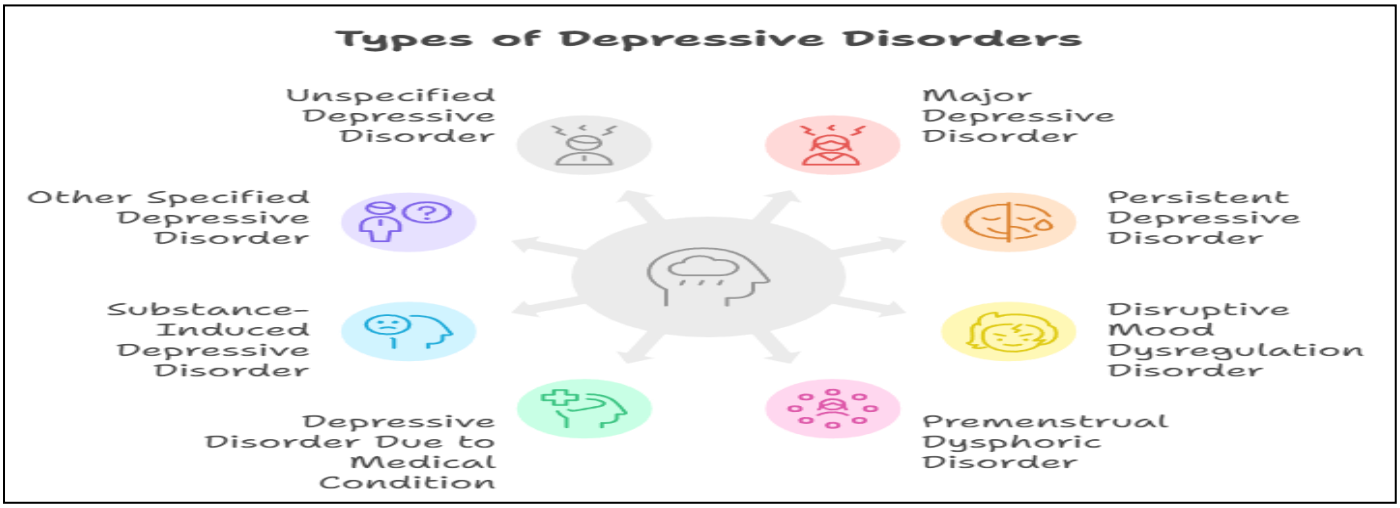

Fig 4 Types of Depressive Disorders

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V. ETIOLOGY AND PATHOPHYSIOLOGY OF DEPRESSION

Depression has a complex etiology that results from interactions between genetic predisposition, environmental exposures, psychosocial stresses, and neurobiological changes (49). Depression risk is significantly influenced by genetic factors; recent genome-wide association studies have identified several susceptibility loci linked to neurotransmission and stress-response pathways, and family and twin studies have shown heritability estimates of roughly 35–40% (50). Stressors that occur early in life, such as abuse, neglect, or extended family dysfunction, alter stress management systems throughout time and raise the risk of depressive episodes in adulthood (51). Socioeconomic hardship, unemployment, and interpersonal conflict are examples of chronic psychosocial stresses that can precipitate depressive episodes in susceptible people (52). Numerous pharmacotherapies are based on the dysregulation of monoamine neurotransmitter systems, particularly serotonin, norepinephrine, and dopamine, which has been linked to the pathophysiology of depression (53). Beyond monoamines, disruptions in GABAergic and glutamatergic signaling have been identified more often, and glutamate-modulating therapies have shown quick antidepressant effects in certain individuals (54). Patients with depression frequently exhibit hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which is characterized by persistent increases in cortisol and compromised negative feedback. This hyperactivity leads to neuronal atrophy, especially in the hippocampus (55). In addition to influencing neurotransmitter metabolism and neuroplasticity, neuroinflammatory processes marked by increased pro-inflammatory cytokines (such as TNF-α and IL-6) and microglia activation are linked to depressive symptoms (56). The cognitive and affective disorders associated with depression are caused by structural and functional alterations in the brain, such as decreased hippocampus volume, prefrontal cortical thinning, and modified amygdala reactivity (57). Deficits in neuroplasticity, such as reduced expression of brain-derived neurotrophic factor (BDNF) and defective synaptogenesis, are linked to the chronicity and recurrence of depression (58).Through inflammatory, endocrine, and neurochemical pathways, some drugs and medical comorbidities (such as diabetes, cardiovascular disease, and chronic pain) can both cause and exacerbate depressed symptoms (59). Neurobiological susceptibility can be made worse and rehabilitation hampered by substance abuse (alcohol, sedatives, and illegal drugs) and poor lifestyle variables (sleep disturbance, sedentary activity, and poor diet) (60).

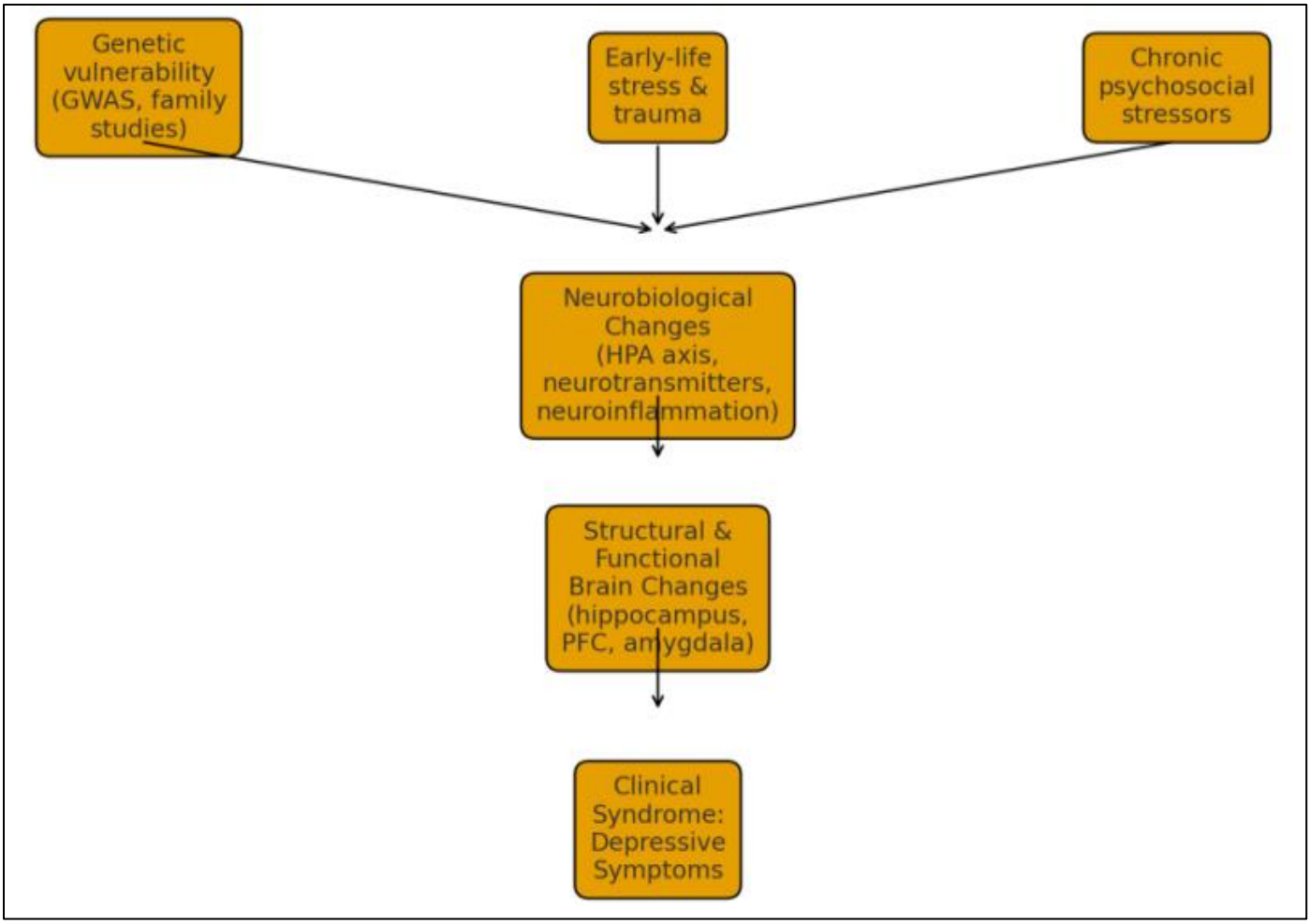

Fig 5 Etiology of Depression

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VI. DIAGNOSIS OF DEPRESSION

Due to the lack of a single confirmed laboratory or imaging test, depression is diagnosed clinically using validated diagnostic criteria, mental state evaluation, and history (61). In order to standardize diagnosis across settings, both the DSM-5 and ICD-11 offer symptom clusters, duration thresholds, and impairment requirements (62).

- *DSM-5 Diagnostic Framework:*

Major Depressive Disorder (MDD) is defined by the DSM-5 as having at least five symptoms over the course of two weeks, one of which must be a depressed mood or a considerably impaired interest or pleasure. Significant changes in weight or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, exhaustion, decreased focus or indecision, feelings of worthlessness or excessive guilt, and repeated thoughts of death or suicide ideation or attempt are among the qualifying symptoms. To satisfy the DSM-5 criterion, symptoms must result in clinically substantial distress or functional impairment in social, academic, or vocational domains. For a diagnosis of unipolar MDD, there must never have been a manic or hypomanic episode, and the illness cannot be better explained by the effects of substances or medications,In order to improve clinical description and direct treatment planning, the DSM-5 additionally permits specifiers (e.g., with anxious discomfort,melancholy features, atypical features, psychotic features, peripartum onset, seasonal pattern) and episode intensity ratings (mild, moderate, severe) (61).

- *ICD-11 Diagnostic Framework:*

A depressive episode is defined by ICD-11 as lasting at least two weeks and characterized by persistent low mood, diminished interest, and decreased energy, along with other symptoms like poor concentration, low self-esteem, guilt, hopelessness, sleep disturbance, and changes in appetite (62). ICD-11 provides a comparable framework to DSM-5 while standardizing worldwide reporting by classifying severity (mild, moderate, and severe) based on the number of symptoms and degree of functional impairment. Additionally, ICD-11 allows course qualifiers and related criteria to capture clinical variability in public health and routine care settings.

- *Clinical Interview and Mental-Status Examination:*

To define syndrome borders and rule out mimics, a structured clinical interview records onset, duration, course (single vs. recurrent), precipitants, psychosocial stresses, and personal and family psychiatric history (63). In order to confirm or deny a depressive condition, the mental-status evaluation methodically evaluates mood/affect, thought content (such as guilt, worthlessness, and hopelessness), cognition (attention, memory, executive function), psychomotor abnormalities, and suicidality. In busy environments, using structured diagnostic interviews like the SCID-5 or the MINI can improve reliability and decrease overdiagnosis or underdiagnosis (64).

- *Screening and Case-Finding (Not Diagnostic Alone):*

The PHQ-2 is frequently used as a preliminary measure prior to a comprehensive PHQ-9 in order to identify patients who require a thorough diagnostic examination (65). Although a clinical interview is still necessary for diagnosis, the PHQ-9 has been validated for use in primary care and specialist settings for screening and tracking severity over time. Meta-analyses have shown good sensitivity and specificity across cut-offs. The detection and monitoring of depressive disorders at scale can be enhanced by the routine use of validated screening in systems with diagnostic confirmation and follow-up.

- *Clinician-Rated and Self-Report Severity Scales:*

In addition to diagnostic criteria, the Hamilton Depression Rating Scale (HAM-D/HDRS), which is clinician-rated, is frequently used in trials and specialist clinics to measure symptom intensity and therapy response. Another clinician-rated tool with a high sensitivity to change that is useful for tracking treatment progress once a diagnosis is made is the Montgomery-àsberg Depression Rating Scale (MADRS) (66). When used in conjunction with clinical findings, the Beck Depression Inventory-II (BDI-II), a psychometrically sound self-report tool that measures symptom burden, can support collaborative decision-making.

- *Differential Diagnosis (Rule-Outs and Rule-Ins):*

Because antidepressant monotherapy can trigger mania or rapid cycling in bipolar illness, clinicians must distinguish between unipolar depression and bipolar depression. When a patient's history indicates episodicity or family loading, screening tools such as the MDQ and structured probes are crucial (67). The symptoms of normal bereavement, adjustment disorder with depressed mood, persistent depressive disorder, main anxiety disorders, obsessive-compulsive disorder, and trauma-related disorders might overlap and necessitate thorough contextual assessment. Targeted history, examination, and testing are essential since medical mimics include hypothyroidism, anemia, vitamin B12 or folate insufficiency, Parkinson's disease, cerebrovascular illness, obstructive sleep apnea, persistent infections, and drug side effects (68). When timing indicates intoxication, withdrawal, or recent medication changes, substance-induced mood symptoms from alcohol, sedatives, stimulants, corticosteroids, interferons, and other medicines must be taken into account. When formal diagnosis are required at scale in epidemiologic or collaborative-care settings, population instruments such as the CIDI can facilitate standardized ascertainment of depression episodes.

- *Medical Evaluation and Laboratory Tests (to Exclude Contributors):*

Without diagnosing depression itself, a physical examination and problem-focused tests help rule out illnesses that either cause or worsen depressive symptoms. TSH, total blood count, electrolytes, renal/hepatic panels, vitamin B12/folate, and other tests based on clinical indicators (e.g., pregnancy test, inflammatory or viral screens) are common initial labs when the history indicates

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nutritional or neurologic contributions. Instead of being routinely used in simple depressive disorders, neuroimaging is reserved for unusual presentations (e.g., new focal deficits, late-life first episode with cognitive decline, or suspected structural pathology).

➢ *Suicide Risk Assessment and Safety:*

A suicide risk assessment that examines thoughts, intent, plan, means, prior attempts, and protective variables using a structured method, such as the Columbia-Suicide Severity Rating Scale (C-SSRS) when available, must be included of every depressive diagnostic diagnosis (68). Depending on clinical assessment and available resources, high or imminent risk calls for same-day safety planning, means-restriction counseling, urgent psychiatric evaluation, or a higher level of care. Depressive symptoms, functional impairment, and risk assessment should all be clearly linked in the documentation to the immediate management plan and diagnostic impression (69).

➢ *Functional Impairment and Documentation:*

Clinicians should record effects on employment, study, caregiving, and self-care because both DSM-5 and ICD-11 require that symptoms produce clinically substantial impairment. They may also utilize standardized measures like WHODAS 2.0 to quantify disability in longitudinal care. Evidence-based therapy selection and follow-up intervals are guided by clear documentation of episode specifiers, severity, and differential diagnoses, which also enhances communication between providers.

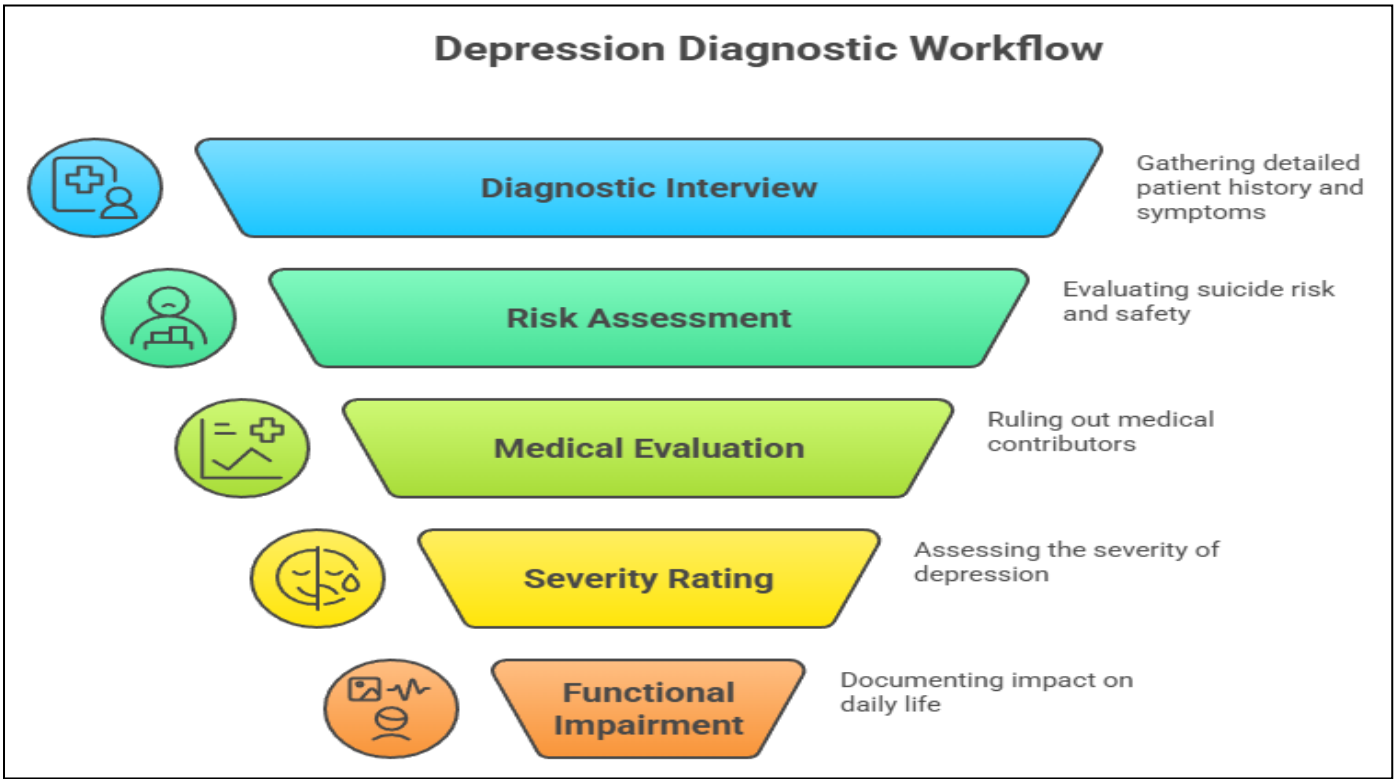

Fig 6 Workflow of Depression Diagnosis

VII. CLASSIFICATION OF ANTIDEPRESSANT DRUGS

Antidepressants are the mainstay of therapy for depression, a serious mental illness that needs pharmaceutical treatment (70). These medications are categorized according to how they affect monoaminergic neurotransmission, primarily the dopamine, serotonin, and norepinephrine pathways (71).

Table 1 Classification of Antidepressant Drugs

Sr.no.	Classification	Meachanisim	Examples	Key Adverse Effects	Reference
1.	**Tricyclic Antidepressants (TCAs)**	TCAs inhibit presynaptic reuptake of norepinephrine and serotonin by blocking norepinephrine transporter (NET) and serotonin transporter (SERT)	Amitriptyline, Imipramine, Clomipramine, Nortriptyline, Desipramine	Dry Mouth, Constipation, Blurred Vision, Urinary Retention	(72)
2.	**Selective Serotonin Reuptake**	SSRIs selectively block serotonin transporter (SERT), preventing reuptake of	Fluoxetine, Sertraline, Paroxetine,	Nausea, Diarrhea	(73).

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	Inhibitors (SSRIs)	serotonin (5-HT) into presynaptic neurons, thereby enhancing serotonergic neurotransmission.	Citalopram		
3.	**Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)**	SNRIs inhibit both SERT and NET, thereby increasing levels of serotonin and norepinephrine in the synaptic cleft [136].	Venlafaxine, duloxetine, desvenlafaxine	nausea, headache, insomnia, and sexual dysfunction similar to SSRIs,	(73).
4.	**Monoamine Oxidase Inhibitors (MAOIs)**	MAOIs irreversibly inhibit the enzyme monoamine oxidase (MAO-A and MAO-B).	Phenelzine, tranylcypromine, isocarboxazid	MAOIs can cause orthostatic hypotension weight gain, insomnia, and sexual dysfunction	(74).
5.	**Atypical / Novel Antidepressants**	**a. Bupropion** Bupropion inhibits norepinephrine transporter (NET) and dopamine transporter (DAT), increasing norepinephrine and dopamine neurotransmission.	Bupropion (commonly used for depression and smoking cessation)	Insomnia, dry mouth, tremors, and risk of seizures at high doses.	(75).
		b. Mirtazapine Mirtazapine acts as an antagonist at presynaptic α2-adrenergic receptors, enhancing norepinephrine and serotonin release.	Mirtazapine	sedation, weight gain, and increased appetite.	
		c. Trazodone Trazodone is a serotonin antagonist and reuptake inhibitor (SARI). It blocks 5-HT2A receptors while weaklyInhibiting serotonin reuptake	Trazodone, nefazodone	dizziness Sedation, orthostatic hypotension	

VIII. ROLE OF THE PHARMACIST IN DEPRESSION MANAGEMENT

➢ *Screening and Early Identification:*

Pharmacists are easily accessible medical specialists who are crucial in diagnosing, tracking, and treating depression (71). Patient education, making sure antidepressants are used safely, monitoring adherence, checking for drug interactions, and referring patients to mental health professionals as needed are all part of their duties (72). Pharmacists help improve treatment outcomes and patient safety in the management of depression by working with doctors and other healthcare professionals (73). By using quick structured instruments (such the PHQ-2/PHQ-9) or by observing symptoms, pharmacists can identify patients who may be at risk for depression and direct them to the proper medical services (74). Pharmacists can minimize delays in diagnosis and therapy initiation by detecting problems early (75).

➢ *Patient Education and Counselling:*

Pharmacists offer antidepressant therapy counseling, outlining the anticipated beginning of action, potential side effects, significance of adherence, and safe cessation (76). Patient comprehension and acceptance of treatment are enhanced by clear instruction, which results in improved adherence.

➢ *Medication Optimization and Safety:*

Pharmacists check prescriptions for medication-drug interactions, contraindications, and proper drug selection and dosage (77). By identifying dangerous combinations of serotonergic medications, they aid in the prevention of major side effects such serotonin syndrome (78). Pharmacists also lower the likelihood of polypharmacy in patients with comorbidities and depression by medication reconciliation (79).

➢ *Adherence Support:*

Antidepressant non-adherence is a significant obstacle to recovery, and pharmacists can enhance adherence through motivational interviews, reminder systems, and follow-up consultations (80). Pharmacist interventions considerably improve treatment duration and adherence in depression, according to research (81).

➢ *Monitoring and Management of Adverse Effects:*

Pharmacists keep an eye out for side effects such sleep difficulties, weight gain, gastrointestinal distress, and sexual dysfunction. In order to prevent withdrawal symptoms, they also offer advice on how to safely taper off antidepressants. Patients on SNRIs should have their blood pressure monitored, and elderly SSRI users should have their electrolytes evaluated (82).

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➢ *Suicide Risk Recognition and Referral:*

Pharmacists are trained to quickly send patients who exhibit warning symptoms of suicide thoughts to emergency or psychiatric care. Pharmacists may be the first healthcare providers in community settings, so this role is especially crucial (83).

➢ *Collaborative Care:*

In multidisciplinary teams, pharmacists facilitate shared decision-making between patients and prescribers, optimize regimens, and offer medication expertise. It has been demonstrated that collaborative care models involving pharmacists enhance clinical outcomes and adherence.

➢ *Public Health and Stigma Reduction:*

Pharmacists support patients with depression by offering community services, raising awareness of mental health issues, and taking part in initiatives to lessen stigma.

Pharmacists play a variety of roles in managing depression, such as screening, counseling, adherence assistance, safety monitoring, crisis referral, and involvement in collaborative care teams. Increasing the use of pharmacist-led interventions in the treatment of depression can enhance treatment results, lessen stigma, and close gaps in mental health services (84).

IX. RECENT ADVANCES AND FUTURE DIRECTIONS

➢ *Recent Advances:*

- *Rapid-Acting Pharmacotherapies:*

The capacity of ketamine, an NMDA receptor antagonist, to provide quick relief within hours of injection has made it a breakthrough in the treatment of depression, especially in instances that are resistant to treatment (85). Esketamine, its S-enantiomer, is available as an intranasal formulation and has received regulatory permission for use as an adjuvant treatment for resistant depression in a number of nations (86). Beyond ketamine, psychedelic-assisted treatments like psilocybin are promising because they improve connectivity within brain networks linked to mood regulation and induce neuroplastic changes (87). Significant symptom reduction is reported in clinical trials, frequently following just one or two guided sessions (88).

- *Neuromodulation Therapies:*

There is increasing evidence that repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation method, is safe and effective in treating depression (89). Theta-burst stimulation and expedited TMS protocols are examples of recent advancements that can reduce treatment duration from many weeks to a few days without sacrificing clinical efficacy (90). By concentrating stimulation on specific brain regions, MRI-guided targeting and neuronavigation are further enhancing the accuracy and results of TMS (91).

- *Biomarkers and Inflammation:*

With increased cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) associated with depressed symptoms and a poor response to traditional antidepressants, there is mounting evidence that inflammation plays a role in depression (92). Research on anti-inflammatory medicines and repurposed medications for patient subgroups with elevated inflammatory markers has been stimulated as a result (93). Furthermore, genetic polymorphisms, neuroimaging signals, and brain-derived neurotrophic factor (BDNF) are being investigated as biomarkers to guide individualized therapy and predict treatment response (94).

- *Digital Therapeutics:*

Digital health tools, such as internet-delivered cognitive behavioral therapy (iCBT) and smartphone apps, are becoming more widely acknowledged as useful supplements in the treatment of depression (95). When paired with normal care, phase-3 trials of prescription digital therapies like CT-152 demonstrate a significant reduction in symptoms (96). Additionally, AI-powered platforms are being created to track patient behavior, anticipate relapses, and customize treatments in real time (97).

- *Comparative Effectiveness:*

Electroconvulsive therapy (ECT), ketamine, psilocybin, and rTMS may offer better short-term results than conventional antidepressants, particularly in treatment-resistant groups, according to recent network meta-analyses. But each treatment has its own drawbacks: psilocybin needs certain clinical settings, ketamine has the potential to be abused, and ECT has cognitive side effects. This emphasizes the necessity of customized treatment planning to strike a balance between accessibility, safety, and efficacy (98).

➢ *Future Directions:*

Personalized medicine, where biomarkers direct physicians to the best course of action for each patient, is the way of the future for treating depression. It is crucial to continue optimizing fast-acting drugs, including safe long-term maintenance techniques for psilocybin and ketamine. It is anticipated that developments in neuromodulation, such as focused and faster TMS protocols, would increase clinical accessibility. Another interesting approach is the development of immune-modulating treatments for patients with high inflammatory markers. Lastly, incorporating digital and AI-driven therapies into standard psychiatric care may transform ongoing monitoring and early detection, improving results and lowering relapse rates (99).

X. CONCLUSION

One of the main causes of disability and a lower quality of life globally is depression, a complicated and multidimensional mental health condition. Even though many patients have found comfort with traditional antidepressants, their drawbacks such as delayed onset, adverse effects, and limited efficacy in cases that are resistant to treatment highlight the critical need for novel strategies. Rapid-acting medications, such as psilocybin,

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ketamine, and esketamine, have given rise to new hope by relieving symptoms more quickly than conventional treatments.By offering efficient, non-invasive alternatives, neuromodulation techniques like repetitive transcranial magnetic stimulation (rTMS) and more recent accelerated protocols are increasing therapy options. Alongside these advancements, the identification of biomarkers and the connection between inflammation and depression have paved the way for precision medicine, which allows for the customization of treatment based on a patient's biologicalprofile.With the emergence of digital cognitive behavioral therapy, mobile health apps, and AI-based monitoring systems, the digital revolution has further improved depression treatment by facilitating ongoing care and early relapse prevention. In addition to boosting treatment results, these advancements are changing how depression is identified, tracked, and treated. Accessible, individualized, and integrated care will be crucial for managing depression in the future. Healthcare professionals can get closer to providing quicker, safer, and more effective treatment alternatives by integrating pharmaceutical advancements, neuromodulation, biomarker-guided therapies, and digital therapeutics. These advancements give pharmacy professionals the chance to make significant contributions to patient care, research, and teaching, making them important players in reducing the prevalence of depression worldwide. In conclusion, the changing field of depression therapy emphasizes a move away from a "one-size-fits-all" strategy and toward individualized, creative, and patient-centered care. This change offers better clinical results as well as a better future for those who are depressed.

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