WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 11, 2033-2055. Review Article ISSN 2277–7105

PHENOTHIAZINES AS PROMISING AGENTS IN THE MANAGEMENT OF DEPRESSION

Lagad Madhuri*, Dr. Mayur S. Bhosale, Avhad Swapnali

Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Pravaranagar, Loni, Tal-Rahata, Dist-Ahilyanagar-413736, Maharashtra, India.

Article Received on 05 May 2026,
Article Revised on 25 May 2026,
Article Published on 03 June 2026,

https://doi.org/10.5281/zenodo.20535769

***Corresponding Author**
Lagad Madhuri
Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Pravaranagar, Loni, Tal-Rahata, Dist-Ahilyanagar-413736, Maharashtra, India.

How to cite this Article: Lagad Madhuri*, Dr. Mayur S. Bhosale, Avhad Swapnali (2026). Phenothiazines As Promising Agents In The Management Of Depression. World Journal of Pharmaceutical Research, 15(11), 2033–2055.

ABSTRACT

Depression, or Major Depressive Disorder (MDD), is a common and serious psychiatric disorder characterized by persistent sadness, loss of interest, and cognitive and physical disturbances. Despite the availability of several antidepressant drugs such as SSRIs, SNRIs, TCAs, and MAOIs, many patients experience delayed response, adverse effects, or treatment resistance. Therefore, the search for new therapeutic strategies remains essential. Phenothiazine, a tricyclic heterocyclic scaffold containing nitrogen and sulfur atoms, has long been used in medicinal chemistry, particularly for antipsychotic and antihistaminic drugs. Recent studies suggest that certain phenothiazine derivatives may exhibit antidepressant potential by modulating multiple neurotransmitter systems including dopamine, serotonin, and norepinephrine. This review highlights the neurobiology of depression, structural features and synthesis of phenothiazine, structure–activity relationships, mechanisms contributing to antidepressant effects, and preclinical evaluation models. It also discusses the current clinical status and future prospects of phenothiazine-based compounds in antidepressant drug development.

KEYWORDS: Depression; Phenothiazine derivatives; Structure–activity relationship; Antidepressant activity; Neurotransmitter modulation; Preclinical models.

INTRODUCTION

1. OVERVIEW OF DEPRESSION

Depression, clinically referred to as **Major Depressive Disorder (MDD)**, is a chronic, recurrent, and potentially life-threatening psychiatric disorder characterized by persistent low mood, anhedonia, cognitive impairment, and somatic disturbances.[1] It is distinct from transient emotional responses to stress, as it involves sustained alterations in mood, motivation, behavior, and neurobiological function that significantly impair social and occupational performance.[2]

Depression is one of the most prevalent psychiatric disorders worldwide and constitutes a major contributor to the global burden of disease.[3] According to the World Health Organization (WHO), approximately 280 million people globally are affected by depressive disorders, with an estimated point prevalence of around 3–5% in the general population. The disorder affects individuals across all age groups, cultures, and socioeconomic strata, with consistently higher prevalence observed among women compared to men.[4] Epidemiological findings from the Institute for Health Metrics and Evaluation through the Global Burden of Disease (GBD) study further demonstrate that depressive disorders rank among the leading causes of years lived with disability (YLDs) worldwide. Lifetime prevalence estimates range between 10–20% in many countries, while 12-month prevalence rates typically range from 5–7%. Regional variations exist, influenced by cultural, economic, and healthcare-related factors; however, underdiagnosis and substantial treatment gaps remain major concerns, particularly in low- and middle-income countries. Collectively, these data underscore the widespread and persistent public health impact of depression at a global level.[5]

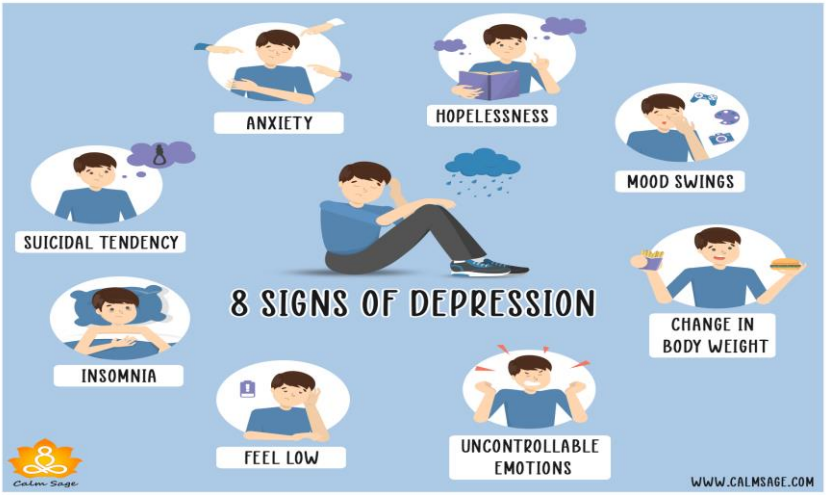


Fig.1:- Sign of Depression.

Clinically, depression is characterized by a constellation of emotional, cognitive, behavioral, and physical symptoms. Core features include persistent sadness, loss of interest or pleasure (anhedonia), fatigue, sleep disturbances, appetite changes, impaired concentration, feelings of worthlessness, psychomotor alterations, and recurrent thoughts of death.[6] The disorder may present in episodic or chronic forms and can vary in severity from mild to severe with psychotic features.[7] Depressive disorders present in several subtypes, including **major depressive disorder**, **persistent depressive disorder (dysthymia)**, **bipolar depression**, **seasonal affective disorder**, and **postpartum depression**.[8]

The etiology of depression is multifactorial, involving complex interactions between genetic vulnerability, environmental stressors, and neurobiological dysregulation.[9] Family and twin studies indicate a significant hereditary component, while psychosocial stress, trauma, chronic illness, and substance abuse act as precipitating factors.[10][11] Neurobiologically, depression has long been associated with the monoamine hypothesis, which proposes that deficiencies in neurotransmitters such as serotonin (5-HT), norepinephrine (NE), and dopamine (DA) contribute to depressive symptomatology. However, contemporary research suggests that depression extends beyond simple neurotransmitter imbalance.[12] [13]

Emerging evidence highlights the involvement of hypothalamic–pituitary–adrenal (HPA) axis hyperactivity, neuroinflammation, oxidative stress, mitochondrial dysfunction, and impaired neuroplasticity in the pathogenesis of depression.[14][15] Reduced levels of brain-derived neurotrophic factor (BDNF) and hippocampal atrophy have been observed in depressed individuals, supporting the neurotrophic hypothesis.[16] Additionally, alterations in glutamatergic and GABAergic signaling pathways have gained attention as novel therapeutic targets.[17]

Despite the availability of multiple antidepressant classes—including selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs)—treatment outcomes remain suboptimal.[18] A significant proportion of patients exhibit delayed therapeutic response, incomplete remission, or treatment resistance.[19] [20] Furthermore, conventional antidepressants are associated with adverse effects such as weight gain, sexual dysfunction, gastrointestinal disturbances, and cardiovascular complications, which limit adherence.[21]

These limitations underscore the need for novel therapeutic agents with improved efficacy, faster onset of action, and better safety profiles.[22] Ongoing research is directed toward the development of multi-target therapeutic agents, enhancement of neuroplasticity mechanisms, implementation of anti-inflammatory interventions, and the repurposing of existing drug scaffolds for improved antidepressant efficacy.[23] In this context, heterocyclic compounds and structurally diverse pharmacophores are being explored for their potential antidepressant properties.[24]

2. Phenothiazine Scaffold: A Versatile Platform for Drug Development

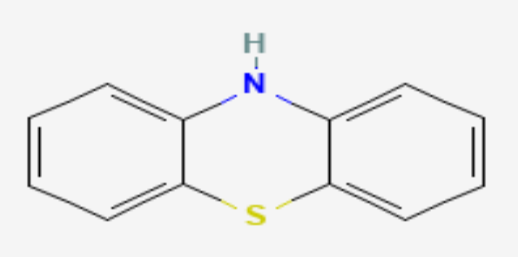


Fig.2 :- Phenothiazine.

Phenothiazine is a nitrogen- and sulphur-containing tricyclic heterocyclic compound characterized by a dibenzothiazine core structure. The phenothiazine scaffold consists of two benzene rings fused to a central thiazine ring, conferring unique physicochemical and pharmacological properties. Owing to its versatile chemical reactivity and structural flexibility, phenothiazine serves as a privileged scaffold in medicinal chemistry and drug design.[25][26]

Historically, phenothiazine derivatives gained prominence in the early 20th century as synthetic dyes and antihistaminic agents.[27] The discovery of **Chlorpromazine** in the 1950s revolutionized psychiatric treatment, marking the advent of modern psychopharmacology. Chlorpromazine became the first widely used antipsychotic drug for the management of schizophrenia and other psychotic disorders, primarily through dopamine D_2 receptor antagonism. This breakthrough established phenothiazines as a major class of neuroleptic agents.[28][29]

Structurally, substitution at the nitrogen atom (position-10) and at the aromatic rings significantly influences biological activity.[30] Based on the side-chain variations at position-10, phenothiazines are broadly classified into three categories.

1. **Aliphatic derivatives** (e.g., **Chlorpromazine**)
2. **Piperazine derivatives** (e.g., **Trifluoperazine**)
3. **Piperidine derivatives** (e.g., **Thioridazine**)[31]

Beyond antipsychotic activity, phenothiazine derivatives exhibit a broad spectrum of pharmacological effects, including antihistaminic, antiemetic, anticholinergic, antimicrobial, anticancer, antioxidant, and potential antidepressant activities.[32] Recent research has expanded interest in phenothiazine analogues due to their ability to modulate multiple molecular targets, including dopaminergic, serotonergic, adrenergic, and glutamatergic systems.[33]

In addition to central nervous system applications, phenothiazine derivatives have demonstrated promising roles in oncology, infectious diseases, and neurodegenerative disorders.[34] Their polypharmacological profile, combined with the feasibility of structural modifications, makes phenothiazine a valuable scaffold for the development of novel therapeutic agents.[35]

2.1. Bernthsen Synthesis of Phenothiazine

One of the classical and historically significant approaches for the synthesis of phenothiazine is the **Bernthsen method**, which involves thermal treatment of diphenylamine with elemental sulphur. This reaction represents one of the earliest documented routes for constructing the phenothiazine nucleus and has been applied in industrial production.

Diphenylamine + Sulphur = Phenothiazine

Reaction Concept

- **Substrate:** Diphenylamine
- **Sulphur Source:** Elemental sulphur
- **Reaction Conditions:** Elevated temperature, typically in the range of 180-250 °C
- **Transformation Type:** Cyclization through sulphur incorporation into the aromatic framework.[36]

Mechanistic Outline

Initially, elemental sulphur interacts with diphenylamine to generate a sulphur-containing intermediate. Subsequent electrophilic substitution occurs preferentially at the ortho position of the aromatic ring relative to the amino group. This facilitates intramolecular cyclization,

leading to the formation of the heterocyclic thiazine ring system. Final dehydrogenation and aromatization steps afford the phenothiazine structure.[37]

2.2. Structural Modifications and Structure–Activity Relationship (SAR)

The biological activity of phenothiazine derivatives is strongly influenced by structural modifications, particularly at the nitrogen atom at position-10 (N-10) and substitutions on the aromatic ring at position-2. These modifications affect pharmacological potency, receptor selectivity, lipophilicity, and pharmacokinetic properties, leading to the development of several therapeutically important drugs.[38]

1. Substitution at Position-10 (Side Chain Modifications) Modification at the N-10 position determines the pharmacological profile of phenothiazine derivatives.

- Aliphatic derivatives (e.g., chlorpromazine, promazine) show moderate antipsychotic activity with strong sedative, antihistaminic, and anticholinergic effects and relatively lower extrapyramidal side effects (EPS).
- Piperazine derivatives (e.g., trifluoperazine, perphenazine, fluphenazine) possess high antipsychotic potency due to strong dopamine D_2 receptor antagonism but may cause more extrapyramidal side effects.
- Piperidine derivatives (e.g., thioridazine, mesoridazine) exhibit moderate potency with strong anticholinergic and sedative effects and lower EPS, although some may cause cardiotoxicity.[39]

2. Substitution at Position-2 (Aromatic Ring) Introduction of electron-withdrawing groups such as halogens (Cl, F), trifluoromethyl (CF_3), or alkoxy groups increases antipsychotic potency, enhances lipophilicity, and improves penetration across the blood–brain barrier.[40]
3. Influence of Side Chain Length A three-carbon linker between the phenothiazine nucleus and the terminal amine provides optimal biological activity, while shorter or longer chains reduce receptor binding affinity.[41]
4. Electronic Effects of Substituents Electron-withdrawing substituents increase dopamine receptor antagonism and CNS penetration, influencing antihistaminic, anticholinergic, and α-adrenergic blocking activities.[42]

Overall, structural modifications of the phenothiazine scaffold produce compounds with diverse pharmacological activities, including antipsychotic, antihistaminic, antiemetic, antimicrobial, anticancer, antioxidant, and potential antidepressant effects.

3. Mechanisms Contributing to Antidepressant Effects

Although **phenothiazine derivatives** are primarily known for their antipsychotic properties, several pharmacological mechanisms suggest that they may also contribute to **antidepressant effects**. Depression is a complex neuropsychiatric disorder involving dysregulation of multiple neurotransmitter systems, including **dopamine, serotonin, and norepinephrine**. Phenothiazines interact with several receptor systems in the central nervous system (CNS), which can influence mood, emotional regulation, and behavioral responses. Their **multireceptor activity** and ability to modulate neurotransmitter pathways make them potential candidates for exploring antidepressant mechanisms.[43]

3.1 Dopaminergic Modulation

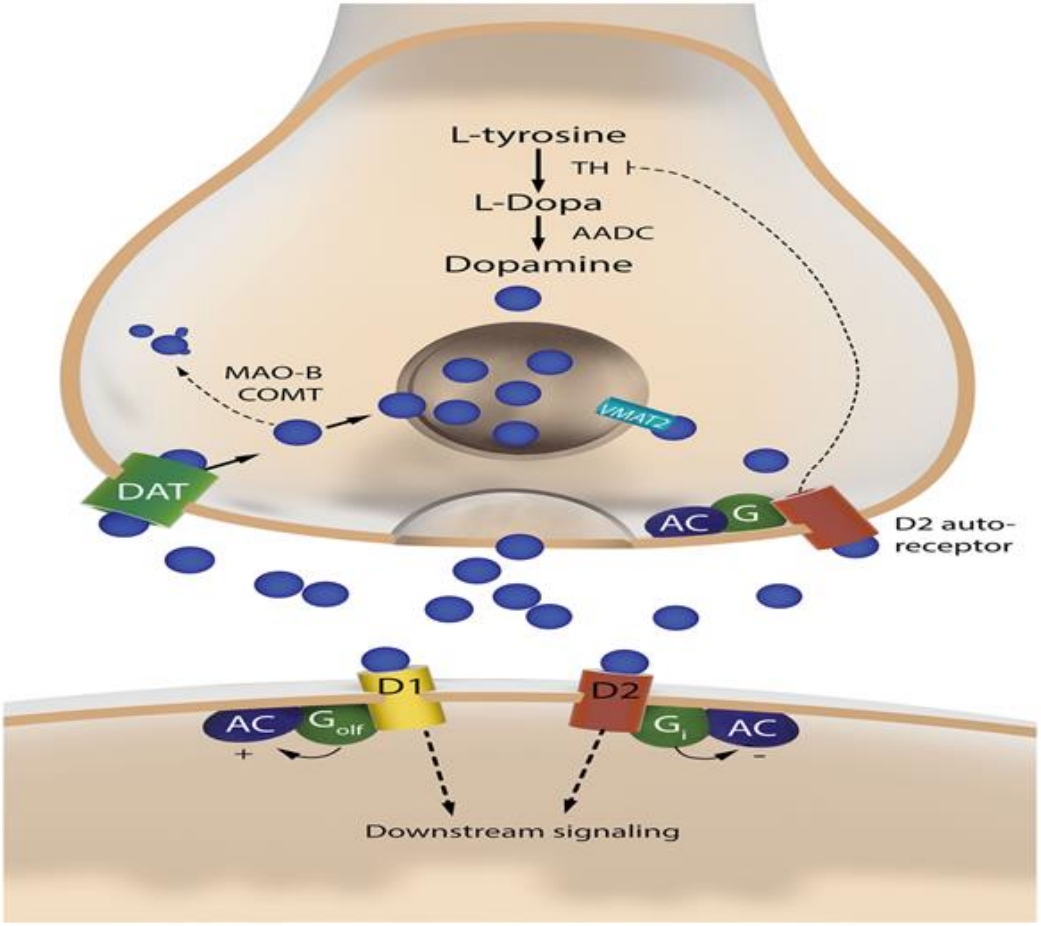


Fig. 3:- Dopamine Signaling Pathway.

Dopamine is an important neurotransmitter involved in motivation, reward, pleasure, and emotional regulation. Reduced dopaminergic activity in the mesolimbic pathway is associated with symptoms of depression such as anhedonia, fatigue, and loss of motivation.

Phenothiazine derivatives interact with dopamine D_2 receptors and act mainly as dopamine receptor antagonists, modifying dopaminergic neurotransmission in the brain.[44]

By regulating dopamine signaling, these compounds can influence the brain's reward circuitry and emotional responses. Controlled modulation of dopamine pathways may help restore balance in neurotransmission and contribute to improvement in mood and motivation, which are essential components in the management of depressive symptoms.[45]

3.2 Serotonergic Regulation

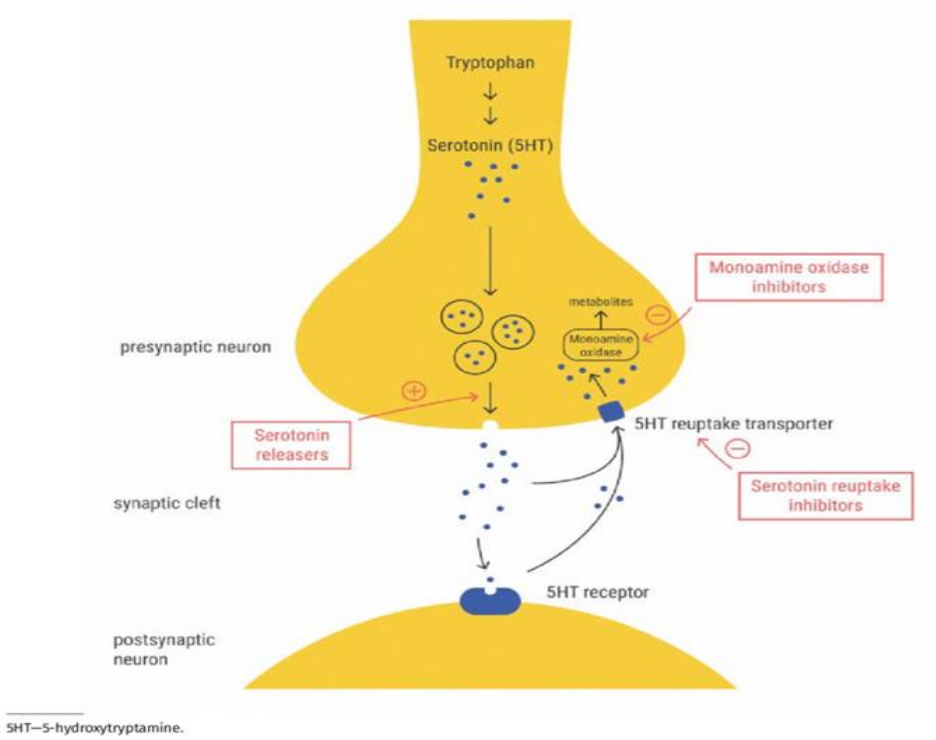


Fig. 4: Serotonin Signaling Pathway.

Serotonin (5-hydroxytryptamine, 5-HT) plays a central role in regulating mood, sleep, appetite, and emotional stability. Many antidepressant drugs work by increasing serotonergic neurotransmission in the brain. Phenothiazine derivatives can interact with serotonin receptors such as 5-HT_2A and 5-HT_2C, which may influence mood regulation.[46]

Antagonism of these serotonin receptors may enhance serotonergic signaling indirectly and reduce symptoms such as anxiety, irritability, and sleep disturbances that frequently accompany depression. This serotonergic modulation contributes to the potential antidepressant-like effects of certain phenothiazine derivatives.[47]

3.3 Noradrenergic Influence

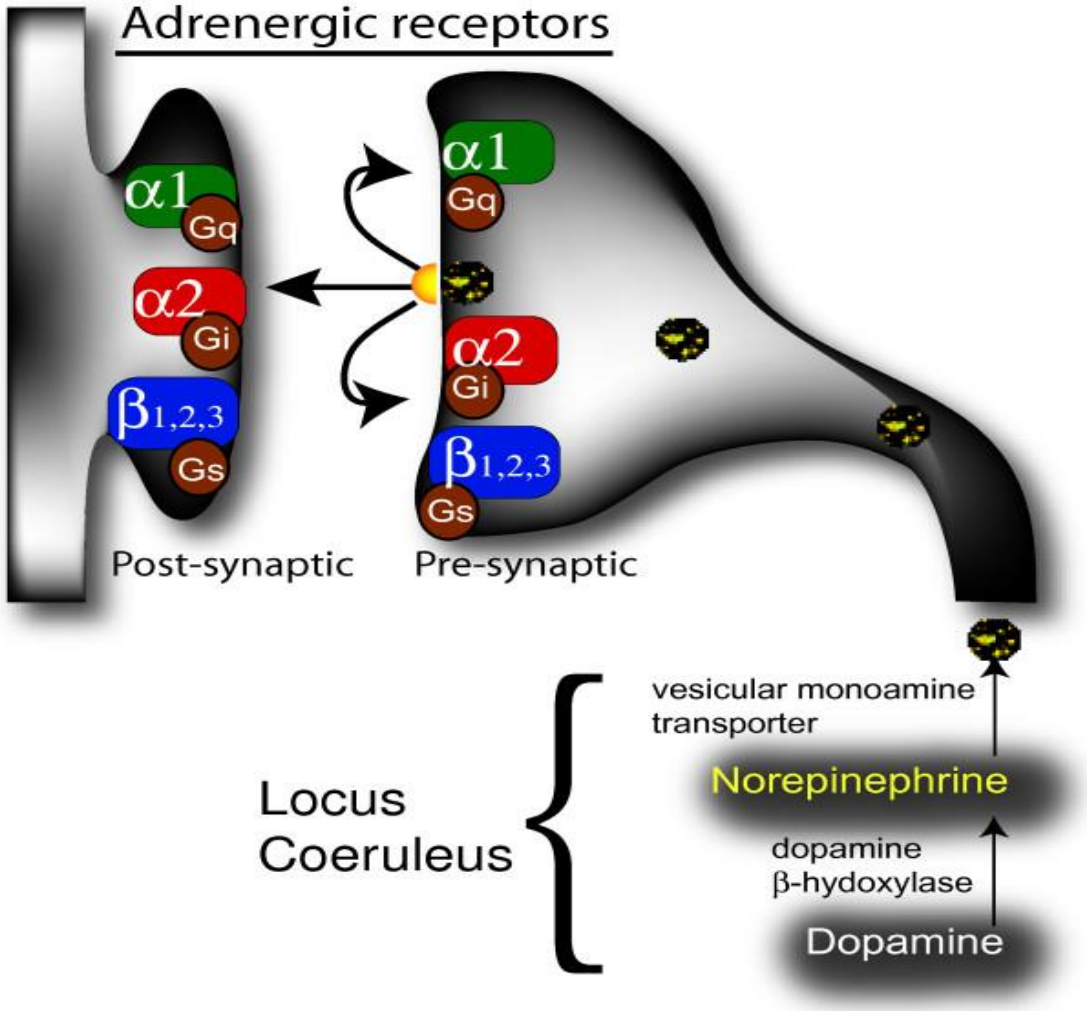


Fig. 5:- Locus Coeruleus-Norepinephrine (LC-NE) System.

The noradrenergic system, originating mainly from the locus coeruleus, regulates alertness, energy levels, and cognitive function. Reduced norepinephrine transmission is associated with low energy, impaired concentration, and psychomotor retardation in depression.[48]

Phenothiazine derivatives may interact with α-adrenergic receptors, particularly α_1 receptors, affecting norepinephrine signaling in the central nervous system. This modulation may help regulate stress responses and emotional processing, which can indirectly support antidepressant activity.[49]

3.4 Histaminergic and Cholinergic Effects

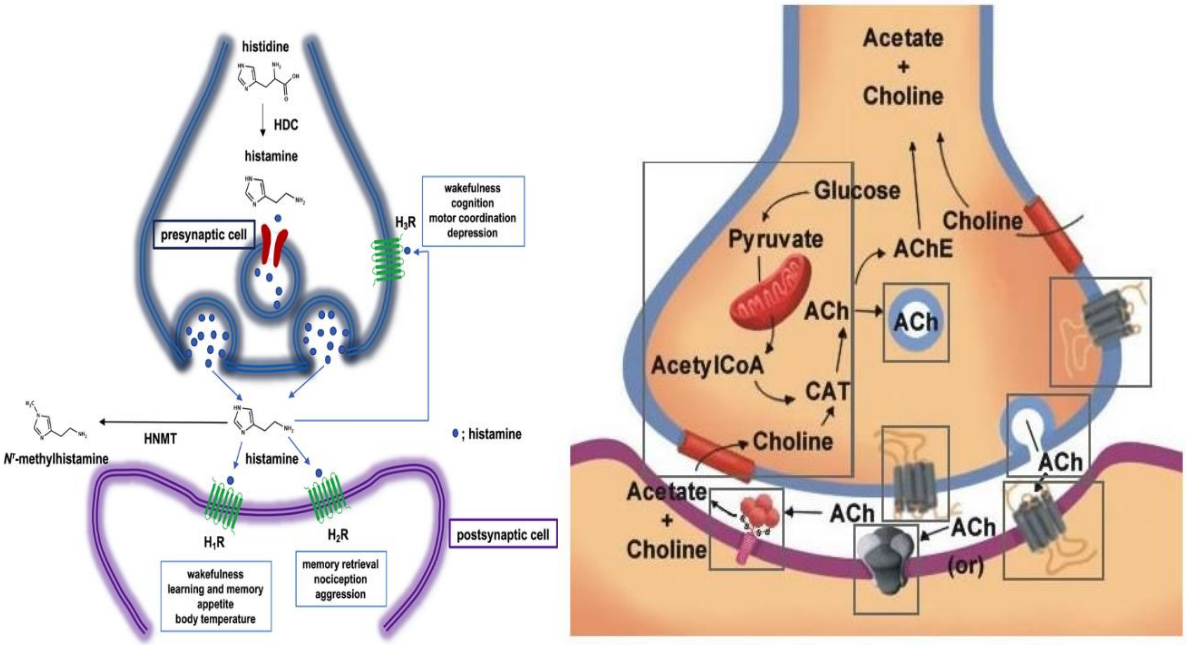


Fig. 6: Histamine Neurotransmission Pathway.

Phenothiazines also interact with **histamine (H_1) and muscarinic acetylcholine receptors** in the brain. Antagonism of **H_1 receptors** produces sedative effects that can improve **sleep disturbances and agitation** often seen in depressive disorders.

Additionally, mild **anticholinergic activity** affects cognitive and emotional processing. Although excessive anticholinergic effects may cause side effects such as dry mouth or blurred vision, moderate modulation of cholinergic pathways can contribute to the overall neurochemical balance involved in mood regulation.[50]

4. Preclinical Assessment of Antidepressant Activity

Preclinical evaluation plays a crucial role in identifying potential antidepressant agents before clinical trials. These studies are typically conducted using animal behavioral models, biochemical assays, and neurochemical analyses to assess the antidepressant-like effects of new compounds. For compounds such as phenothiazine derivatives, preclinical studies help determine their influence on neurotransmitter systems, behavioral responses, and stress-related pathways involved in depression. Commonly used rodent models simulate behavioral and physiological features of depressive disorders and allow researchers to evaluate drug efficacy, mechanism of action, and safety.[51]

4.1 Forced Swim Test (FST)

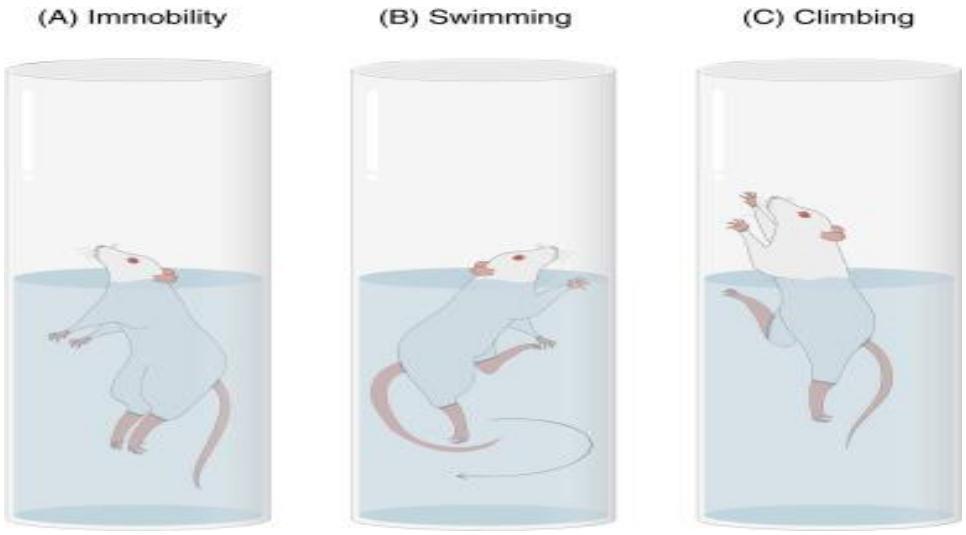


Fig. 7:- Forced Swim Test (FST).

The Forced Swim Test (FST), also known as the Porsolt swim test, is one of the most widely used animal models for screening antidepressant activity. In this method, rodents (rats or mice) are placed in a cylindrical container filled with water, from which escape is impossible. Initially, the animal attempts to escape, but after repeated efforts, it adopts an immobile posture.

The duration of immobility is considered an indicator of behavioral despair. Antidepressant compounds reduce immobility time and increase active behaviors such as swimming or climbing. This model is sensitive to most clinically effective antidepressants, including SSRIs, tricyclic antidepressants, and monoamine oxidase inhibitors.[52]

4.2 Tail Suspension Test (TST)

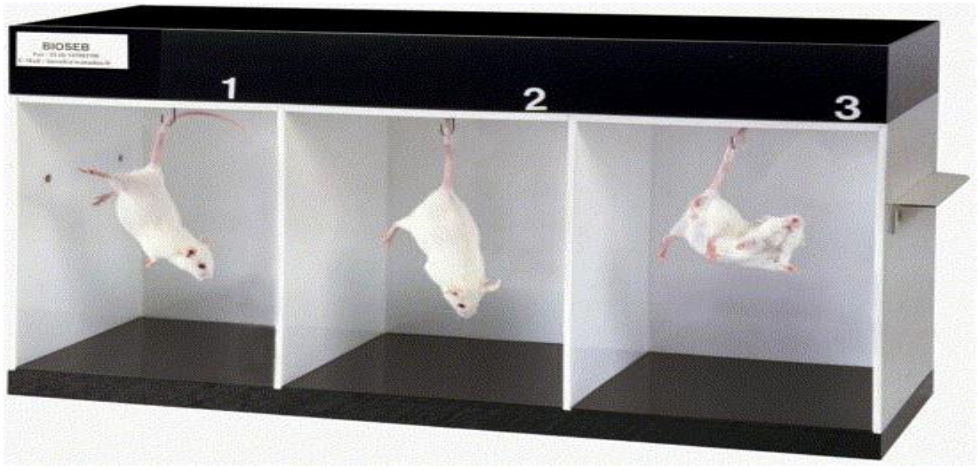


Fig. 8:- Tail Suspension Test (TST)

The Tail Suspension Test (TST) is another commonly used behavioral assay for evaluating antidepressant-like activity in mice. In this test, the mouse is suspended by its tail using adhesive tape attached to a horizontal bar. Initially, the animal shows vigorous escape movements but eventually becomes immobile.

The duration of immobility is recorded over a fixed time period, typically 5–6 minutes. A decrease in immobility time after administration of a test compound suggests antidepressant-like activity. The TST is considered a rapid and reliable screening method for identifying compounds that influence monoaminergic neurotransmission.[53]

4.3 Elevated Plus Maze (EPM)

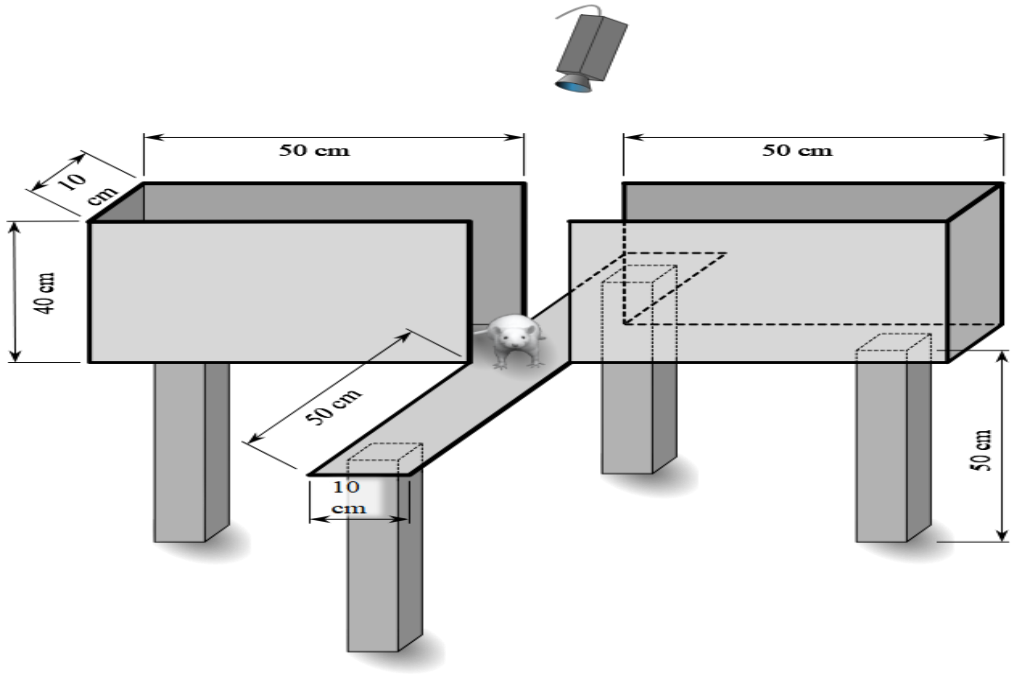


Fig.9: - Elevated Plus Maze (EPM).

The **Elevated Plus Maze (EPM)** is primarily used to evaluate **anxiety-related behavior**, but it is also useful in assessing the anxiolytic and antidepressant potential of compounds. The apparatus consists of **two open arms and two closed arms** elevated above the floor.

Rodents naturally avoid open spaces due to fear of predators. Therefore, increased **time spent in open arms** after drug administration indicates reduced anxiety or improved mood-related behavior. Since anxiety and depression are often comorbid disorders, the EPM test is frequently included in preclinical studies evaluating potential antidepressant agents.[54]

4.4 Open Field Test (OFT)

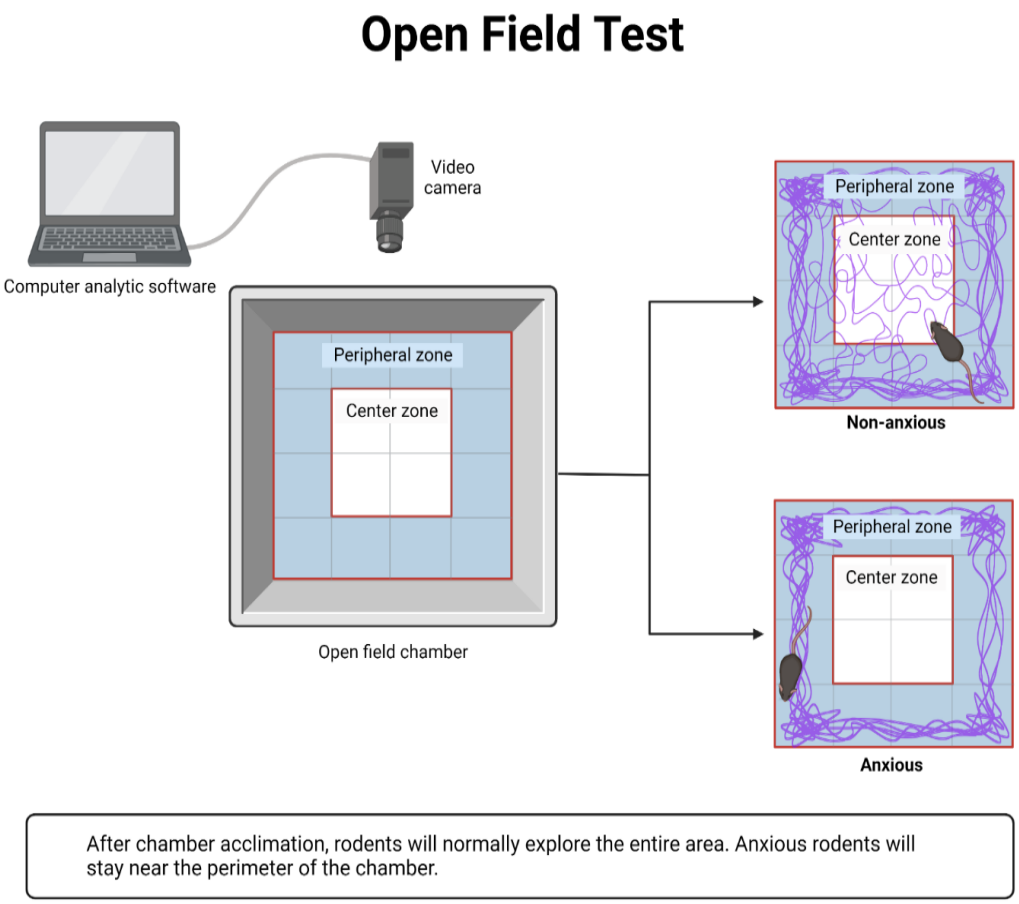


Fig. 10: - Open Field Test (OFT).

The Open Field Test (OFT) is used to measure locomotor activity, exploratory behavior, and emotional responses in rodents. The apparatus typically consists of a large square arena divided into smaller grids.

Animals treated with antidepressant agents generally show increased locomotion, exploration, and time spent in the central area of the field. This test helps differentiate whether a compound's effects are due to true antidepressant activity or simply stimulation of motor activity.[55]

4.5 Biochemical and Neurochemical Analysis

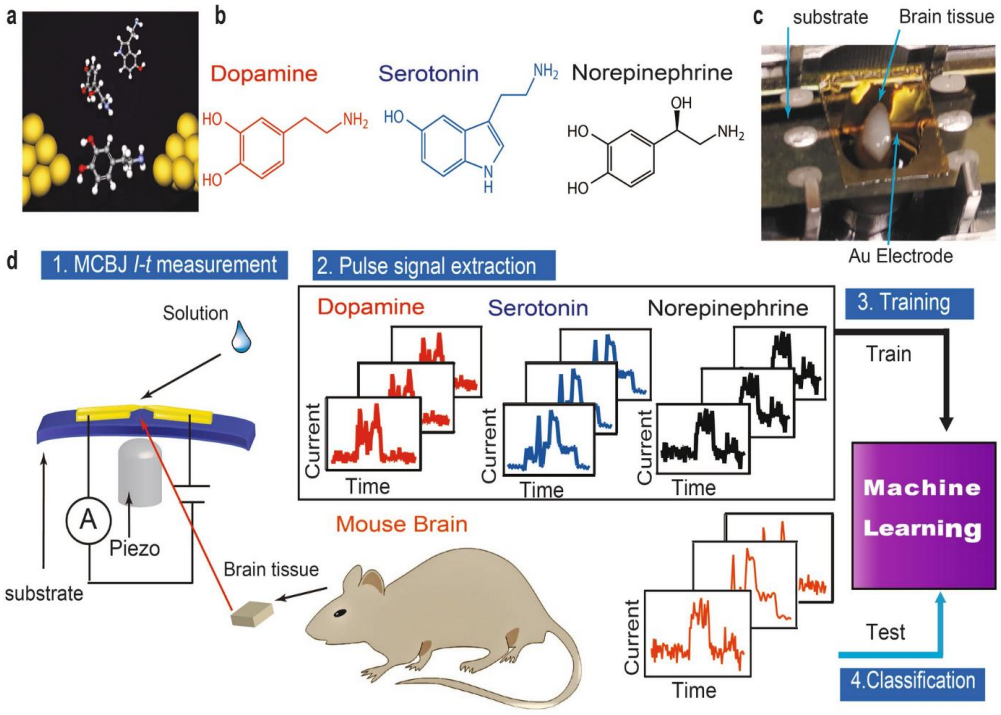


Fig. 11: - Biochemical and Neurochemical Analysis.

In addition to behavioral tests, biochemical studies are performed to evaluate the neurochemical mechanisms underlying antidepressant activity. These analyses often measure levels of dopamine, serotonin, and norepinephrine in different regions of the brain using techniques such as high-performance liquid chromatography (HPLC) or enzyme assays.

Researchers may also evaluate oxidative stress markers, inflammatory cytokines, and neurotrophic factors such as brain-derived neurotrophic factor (BDNF). Changes in these biochemical parameters provide insights into how a test compound affects neuronal function, synaptic plasticity, and stress responses, which are key factors in the pathophysiology of depression.[56]

5. Current Status and Clinical Implications

5.1 Current Clinical Status of Phenothiazine Derivatives

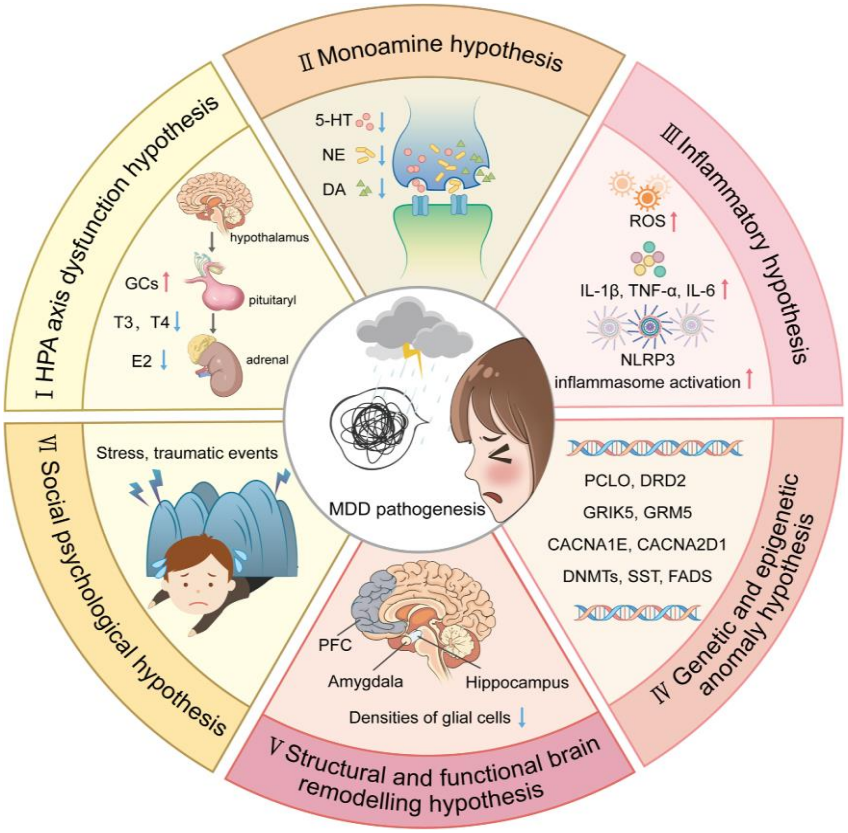
Phenothiazine derivatives represent an important class of **tricyclic heterocyclic compounds** widely used in clinical medicine. Historically, these compounds were primarily developed as **antipsychotic and antihistaminic agents**, with drugs such as chlorpromazine, thioridazine, and promethazine being extensively used for the treatment of **schizophrenia, psychosis, allergies, and nausea**. Their therapeutic effects mainly arise from **dopamine D_2 receptor**

antagonism and interactions with multiple neurotransmitter receptors in the central nervous system.[57]

Although phenothiazines are not considered **first-line antidepressant drugs**, several studies have suggested that certain derivatives exhibit **antidepressant-like activity** due to their ability to modulate **dopaminergic, serotonergic, and adrenergic neurotransmission**. Because depression involves multiple neurotransmitter systems, the **multireceptor pharmacological profile** of phenothiazines has attracted interest in recent pharmacological research.[58]

Currently, phenothiazine derivatives are sometimes used **adjunctively in psychiatric therapy**, particularly in patients experiencing **severe depression accompanied by psychotic symptoms, agitation, or anxiety**. However, their use in depression is generally limited due to the availability of newer antidepressants with improved safety profiles.[59]

5.2 Clinical Implications in Depression Management



The complex neurobiology of depression involves disturbances in several **monoaminergic neurotransmitter systems**, including **serotonin, dopamine, and norepinephrine**.

Phenothiazine derivatives influence these systems through their interaction with **multiple receptor types**, which may contribute to mood stabilization and emotional regulation.

From a clinical perspective, phenothiazines may provide several potential benefits in specific psychiatric conditions.

- **Adjunct therapy in treatment-resistant depression.**
- Management of **psychotic depression.**
- Reduction of **anxiety, agitation, and insomnia** associated with depressive disorders.
- Stabilization of **mood and behavioral disturbances.**

However, their clinical use must be carefully monitored because phenothiazines may produce **adverse effects**, including sedation, anticholinergic effects, orthostatic hypotension, and **extrapyramidal symptoms (EPS)** due to dopamine receptor blockade.[60]

5.3 Limitations and Safety Considerations

Despite their pharmacological potential, phenothiazines have several **clinical limitations** that restrict their use as antidepressant agents. One of the most significant concerns is the development of **extrapyramidal symptoms**, including dystonia, akathisia, and parkinsonism, which arise from dopamine receptor blockade in the **nigrostriatal pathway**.[61]

Long-term use of certain phenothiazine derivatives may also lead to **tardive dyskinesia**, a serious movement disorder characterized by involuntary muscle movements. Other adverse effects may include **sedation, weight gain, cardiovascular complications, and anticholinergic effects** such as dry mouth and blurred vision.

Because of these potential risks, modern antidepressant therapy often favors **selective serotonin reuptake inhibitors (SSRIs)** and **serotonin–norepinephrine reuptake inhibitors (SNRIs)**, which generally exhibit better tolerability and safety.[62]

6. Future Clinical Perspectives

Recent advances in **medicinal chemistry, computational drug design, and molecular pharmacology** have renewed interest in phenothiazine scaffolds for developing **novel multi-target antidepressant agents**. Researchers are exploring **structural modifications and hybrid molecule strategies** to retain the beneficial pharmacological properties of phenothiazines while minimizing their adverse effects.[63]

Future drug development may focus on designing **phenothiazine-based derivatives with improved receptor selectivity, reduced extrapyramidal toxicity, and enhanced neuroprotective activity**. These optimized compounds could potentially serve as **next-generation CNS therapeutics** with applications not only in depression but also in other neuropsychiatric disorders.

Thus, although traditional phenothiazines are not widely used as primary antidepressants today, their **multifunctional pharmacological profile and versatile chemical structure** continue to provide valuable opportunities for **innovative drug discovery and therapeutic development** in the field of neuropsychopharmacology.[64]

7. CONCLUSION

Depression remains a major global health concern, and current antidepressant therapies often show limitations in efficacy and safety. Phenothiazine derivatives, known for their antipsychotic properties, possess a versatile chemical scaffold capable of interacting with multiple neurotransmitter systems involved in mood regulation. Structural modifications of the phenothiazine nucleus have led to compounds with diverse pharmacological activities, including potential antidepressant effects. Although traditional phenothiazines have certain limitations due to adverse effects, recent advances in medicinal chemistry and drug design provide opportunities to develop safer and more effective phenothiazine-based agents. Thus, phenothiazine continues to be a promising platform for the discovery of novel multi-target therapeutic agents for the management of depression.

REFERENCE

1. Chand SP, Arif H. Depression. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. DOI: https: //www.ncbi.nlm.nih.gov/books/
2. Cui L, Li S, Wang S, Wu X, Liu Y. Major depressive disorder: hypothesis, mechanism, prevention and treatment. *Signal Trans duct Target Ther*, 2024; DOI: 10.1038/s41392-024-01738-y.
3. Rong, J., Wang, X., Cheng, P., Li, D., & Zhao, D. (2025). *Global, regional and national burden of depressive disorders and attributable risk factors, from 1990 to 2021: results from the 2021 Global Burden of Disease study*. The British Journal of Psychiatry, 227(4): 688–697. DOI: 10.1192/bjp.2024.266.

4. Ferrari AJ, et al. *Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010.* Plos Medicine, 2013; 10(11): e1001547. DOI: 10.1371/journal.pmed.1001547
5. O'Connor EA, Perdue LA, Coppola EL, Henninger ML, Thomas RG, Gaynes BN. Depression and Suicide Risk Screening: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA, 20*23; 329(23): 2068–2085. DOI: 10.1001/jama.2023.7787
6. Lam RW, Kennedy SH, McIntyre RS, et al. Clinical features and diagnosis of depressive disorders. In: *Depression: Integrating Science and Clinical Practice*. Oxford University Press; 2018; 23–34. DOI: 10.1093/med/9780198804147.003.0004
7. Gaudiano BA, Young D, Chelminski I, Zimmerman M. Depressive Symptom Profiles and Severity Patterns in Outpatients with Psychotic versus Nonpsychotic Major Depression. *Comprehensive Psychiatry, 20*08; 49(2): 192–200. DOI: 10.1016/j.comppsych.2008.02.007
8. Harald Baumeister & Gordon Parker. *Meta-review of depressive subtyping models.* Journal of Affective Disorders, 2012; 139(2): 126–140. DOI: 10.1016/j.jad.2011.07.015
9. Hettema JM. *The Genetics of Depression: Overview and Recent Findings.* Psychiatric Clinics of North America, 2008; 31(1): 1–15. DOI: 10.1016/j.psc.2007.11.006.
10. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. *American Journal of Psychiatry, 20*00; 157(10): 1552–1562. DOI: 10.1176/appi.ajp.157.10.1552
11. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. *American Journal of Psychiatry.* 1999; 156(6): 837–841. DOI: 10.1176/ajp.156.6.837
12. Cowen PJ, Browning M. *What has serotonin to do with depression?* World Psychiatry, 2015; 14(2): 158–160. DOI: 10.1002/wps.20229
13. Krishnan V, Nestler EJ. *The molecular neurobiology of depression.* Nature, 2008; 455(7215): 894–902. doi: 10.1038/nature07455.
14. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. *Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants.* Nature Medicine, 2016; 22(3): 238–249. DOI: 10.1038/nm.4050
15. Ménard C, Hodes GE, Russo SJ. *Pathogenesis of depression: Insights from human and rodent studies.* Neuroscience, 2016; 321: 138–162. DOI: 10.1016/j.neuroscience.2015.05.053.

16. Maes M, Bocchio Chiavetto L, Bignotti S, et al. *Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression.* Journal of Affective Disorders, 2011; 136(3): 933–939. DOI: 10.1016/j.jad.2011.09.053
17. Sen S, Duman R, Sanacora G. *Serum brain-derived neurotrophic factor, depression, and antidepressant medications: Meta-analyses and implications.* Biological Psychiatry, 2008; 64(6): 527–532. DOI: 10.1016/j.biopsych.2008.05.005
18. Sanacora G, Treccani G, Popoli M. *Towards a glutamate hypothesis of depression: An emerging frontier of neuropsychopharmacology for mood disorders.* Nature Reviews Neuroscience, 2012; 13(1): 47–59. DOI: 10.1038/nrn3134
19. Rush AJ, Trivedi MH, Wisniewski SR, et al. *Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. American Journal of Psychiatry, 2006; 163(11): 1905–1917. DOI: 10.1176/ajp.2006.163.11.1905
20. Fava M, Davidson KG. *Definition and epidemiology of treatment-resistant depression.* Psychiatric Clinics of North America. 1996; 19(2): 179–200. DOI: 10.1016/S0193-953X (05)70341-7
21. Edinoff AN, Ashamalla SA, Galan L, et al. *Selective serotonin reuptake inhibitors and adverse effects: a narrative review.* Neurology International, 2021; 13(3): 387–401. DOI: 10.3390/neurolint13030038
22. Otte C, Gold SM, Penninx BW, et al. *Major depressive disorder.* Nature Reviews Disease Primers, 2016; 2: 16065. DOI: 10.1038/nrdp.2016.65
23. Alcaro A, Panksepp J, Zuanazzi MC. *The Affective Core of Emotion: Linking Pleasure, Subjective Well-Being, and Optimal Neuropsychological Function.* Frontiers in Psychology, 2017; 8: 781. DOI: 10.3389/fpsyg.2017.00781
24. Serafini G, Pompili M, Cortese E, et al. *Exploring the role of heterocyclic compounds and medicinal chemistry in novel antidepressants.* Current Medicinal Chemistry, 2021; 28(30): 6193–6220. DOI: 10.2174/0929867328666210329152824
25. Upadhyay PK, Pathak S, Mishra R, Kumar R, Jain A. A multifaceted scaffold for building bioactive compounds: Phenothiazine. *Current Chemical Letters, 20*21; 10(1): 119–138. DOI: https://doi.org/10.5267/j.ccl.2020.11.002
26. Khan F, Misra R. Recent advances in the development of phenothiazine and its fluorescent derivatives for optoelectronic applications. *Journal of Materials Chemistry C, 20*23; 11(8): 2786–2825.

27. Hagenbach A, Gysin H. Über die Wirkung von Phenothiazin-Derivaten als Antihistaminika. *Helvetica Chimica Acta.* 1949; 32(3): 683–692. DOI: https://doi.org/10.1002/hlca.19490320310
28. Lopez-Muñoz F, Alamo C, Cuenca E, Shen WW, Clervoy P, Rubio G. History of the discovery and clinical introduction of Chlorpromazine. *Annals of Clinical Psychiatry, 20*05; 17(3): 113–135. DOI: https://doi.org/10.1080/10401230591002002
29. Patrick GL., An Introduction to Medicinal Chemistry. 6th ed. Oxford: Oxford University Press; 2017. p. 580–584.
30. Motohashi N, Kawase M, Satoh K, Sakagami H. Biological activity of phenothiazines. *Current Drug Targets, 20*00; 1(3): 237–245. DOI: https://doi.org/10.2174/1389450003349385
31. Pluta K, Morak-Młodawska B, Jeleń M. Recent progress in biological activities of phenothiazines. *European Journal of Medicinal Chemistry, 20*11; 46(8): 3179–3189. DOI: https://doi.org/10.1016/j.ejmech.2011.03.021
32. Upadhyay PK, Pathak S, Mishra R, Kumar R, Jain A. A multifaceted scaffold for building bioactive compounds: Phenothiazine. *Current Chemical Letters, 20*21; 10(1): 119–138. DOI: https://doi.org/10.5267/j.ccl.2020.11.002
33. Ohlow MJ, Moosmann B. Phenothiazine: The seven lives of pharmacology's first lead structure. *Drug Discovery Today, 20*11; 16(3–4): 119–131. DOI: https://doi.org/10.1016/j.drudis.2011.01.001
34. Bernthsen A. Ueber Thiodiphenylamine. *Justus Liebig's Annalen der Chemie.* 1883; 217(1): 1–25. DOI: https://doi.org/10.1002/jlac.18832170102
35. Gilman H, Shirley DA. Phenothiazine. *Organic Syntheses.* 1943; 23: 78–80. DOI: https://doi.org/10.15227/orgsyn.023.0078
36. Katritzky AR, Ramsden CA, Joule JA, Zhdankin VV. *Handbook of Heterocyclic Chemistry.* 3rd ed. Oxford: Elsevier; 2010. p. 364–366. DOI: https://doi.org/10.1016/C2009-0-30468-3
37. Juszczyks A, Gąsiorowski K, Swiatek P, Malinka W, Cieślik-Boczula K, Petrus J, Czarnik-Matusewicz B. Chemical structure of phenothiazines and their biological activity. *Pharmacological Reports, 20*12; 64(1): 16–23. DOI: https://doi.org/10.1016/S1734-1140(12)70726-0
38. Feinberg AP, Snyder SH. Phenothiazine drugs: structure–activity relationships explained by a conformation that mimics dopamine. *Proceedings of the National Academy of*

Sciences of the United States of America. 1975; 72(5): 1899–1903. DOI: https://doi.org/10.1073/pnas.72.5.1899

39. Tiwari D, Thakkar SS, Ray A. Structure-activity relationship in phenothiazine antipsychotic drugs: Molecular orbital calculation, molecular docking and physicochemical parameters. *Indian Journal of Chemistry Section B, 20*18; 57(9): 1194–1202.
40. Shukla D, Azad I, Khan MA, Sheikh SY, Ansari JA, Ahmad N, Khan AR, Hassan F. A comprehensive analysis of the therapeutic potential of N-substituted phenothiazine derivatives in medicinal chemistry. *Mini Reviews in Medicinal Chemistry, 20*25. DOI: https://doi.org/10.2174/0113895575400761251007165058
41. Ronco T, Juul M, Reynier Z, et al. Phenothiazine derivatives: the importance of stereoisomerism in the tolerance and efficacy of antimicrobials. *Indian Journal of Microbiology, 20*24; 64: 743–748. DOI: https://doi.org/10.1007/s12088-024-01309-3
42. Brunton LL, Hilal-Dandan R, Kollmann BC. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 13th ed. New York: McGraw-Hill Education; 2018; 279–283.
43. Juszczyks A, Gąsiorowski K, Świątek P, Malinka W, Cieślik-Boczula K, Petrus J, Czarnik-Matusewicz B. Chemical structure of phenothiazines and their biological activity. *Pharmacological Reports, 20*12; 64(1): 16–23. DOI: https://doi.org/10.1016/S1734-1140(12)70726-0
44. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications.* 4th ed. Cambridge: Cambridge University Press; 2013; 289–295.
45. Grace AA. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nature Reviews Neuroscience, 20*16; 17(8): 524–532. DOI: https://doi.org/10.1038/nrn.2016.57
46. Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D_2 and serotonin 5-HT_2 receptor affinities. *J Pharmocol Exp Ther.* 1989; 251(1): 238–246.
47. Meltzer HY. The role of serotonin in antipsychotic drug action. *Neuropsychopharmacology.* 1999; 21(2): 106S–115S. DOI: https://doi.org/10.1016/S0893-133X(99)00046-9
48. Ressler KJ, Nemeroff CB. Role of norepinephrine in the pathophysiology and treatment of mood disorders. *Biol Psychiatry.* 1999; 46(9): 1219–1233. DOI: https://doi.org/10.1016/S0006-3223(99)00219-6.

49. Richelson E. Receptor pharmacology of neuroleptics: relation to clinical effects. *J Clin Psychiatry.* 1999; 60(10): 5–14.
50. Drevets WC, Furey ML. Replicating the antidepressant efficacy of the muscarinic antagonist scopolamine: clinical and mechanistic insights. *Biol Psychiatry, 20*10; 67(5): 432–438. DOI: https://doi.org/10.1016/j.biopsych.2009.11.012
51. Cryan JF, Mombereau C. In search of a depressed mouse: utility of models for studying depression-related behavior in genetically modified mice. *Molecular Psychiatry, 20*04; 9(4): 326–357. DOI: https://doi.org/10.1038/sj.mp.4001457
52. Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. *Nature.* 1977; 266(5604): 730–732. https://doi.org/10.1038/266730a0
53. Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology.* 1985; 85(3): 367–370. DOI: https://doi.org/10.1007/BF00428203
54. Pellow S, Chopin P, File SE, Briley M. Validation of open: closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. *Journal of Neuroscience Methods.* 1985; 14(3): 149–167. DOI: https://doi.org/10.1016/0165-0270(85)90031-7
55. Prut L, Belzung C. The open field as a paradigm to measure the effects of drugs on anxiety-like behaviours: a review. *European Journal of Pharmacology, 20*03; 463(1–3): 3–33. DOI: https://doi.org/10.1016/S0014-2999(03)01272-X
56. Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature, 20*08; 455(7215): 894–902. DOI: https://doi.org/10.1038/nature07455
57. Juszczyks A, Gąsiorowski K, Świątek P, Malinka W, Cieślik-Boczula K, Petrus J, Czarnik-Matusewicz B. Chemical structure of phenothiazines and their biological activity. *Pharmacological Reports, 20*12; 64(1): 16–23. DOI: https://doi.org/10.1016/S1734-1140(12)70726-0.
58. Singh V, Khanna R, Srivastava VK, Palit G, Shanker K. Synthesis and pharmacological evaluation of some phenothiazines as antidepressants. *Arzneimittel-Forschung.* 1992; 42(3): 277–280.
59. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 4th ed. Cambridge: Cambridge University Press; 2013.
60. Baldessarini RJ. Chemotherapy in Psychiatry: Pharmacologic Basis of Treatments for Major Mental Illness. 3rd ed. New York: Springer; 2013.

61. Tarsy D, Baldessarini RJ. Movement disorders induced by antipsychotic drugs. *New England Journal of Medicine, 200*6; 354(17): 1793–1803. DOI: https://doi.org/10.1056/NEJMra052488
62. Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics: differential risk and clinical implications. *CNS Drugs, 200*7; 21(11): 911–936. DOI: https://doi.org/10.2165/00023210-200721110-00004
63. Varga B, Csonka Á, Csonka A, Molnár J, Amaral L, Spengler G. Possible biological and clinical applications of phenothiazines. *Anticancer Research, 20*17; 37(11): 5983–5993. DOI: https://doi.org/10.21873/anticanres.12045.
64. Shukla D, Azad I, Khan MA, Sheikh SY, Ansari JA, Ahmad N, Khan AR, Hassan F. A comprehensive analysis of the therapeutic potential of N-substituted phenothiazine derivatives in medicinal chemistry. *Mini Reviews in Medicinal Chemistry, 202*5. DOI: https://doi.org/10.2174/0113895575400761251007165O5
65. Pluta K, Morak-Młodawska B, Jeleń M. Recent progress in biological activities of phenothiazines. *European Journal of Medicinal Chemistry, 20*11; 46(8): 3179–3189. DOI: https://doi.org/10.1016/j.ejmech.2011.03.021
66. Patrick GL. *An Introduction to Medicinal Chemistry.* 6th ed. Oxford: Oxford University Press; 2017. p. 580–584. DOI: https://doi.org/10.1093/he/9780198749691.001.0001