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Kaviya K
B.Pharm, M.Pharm.,
Department of Pharmacology,
Pallavan Pharmacy College,
Kolivakkam, Kanchipuram,
Tamil Nadu, India

Dr. S Swarnalatha
Department of Pharmacology,
Pallavan Pharmacy College,
Kolivakkam, Kanchipuram,
Tamil Nadu, India

Corresponding Author:
Kaviya K
B.Pharm, M.Pharm.,
Department of Pharmacology,
Pallavan Pharmacy College,
Kolivakkam, Kanchipuram,
Tamil Nadu, India

Neuropharmacology of anti depressant: Mechanisms of action, drug classes, and future therapeutic avenues

Kaviya K and S Swarnalatha

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Abstract
Depression is a complex and debilitating psychiatric disorder characterized by persistent low mood, anhedonia, and cognitive dysfunction, impacting millions globally. The neuropharmacological basis of antidepressant therapy primarily revolves around the modulation of monoaminergic systems-serotonin, norepinephrine, and dopamine-although recent insights highlight the involvement of glutamatergic, GABAergic, and neuroinflammatory pathways. This review provides a comprehensive overview of traditional antidepressant classes, including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs), as well as atypical agents such as NDRIs, SARIs, and NaSSAs. Furthermore, it delves into cutting-edge developments involving NMDA receptor antagonists and GABAergic modulators that promise faster onset and improved efficacy in treatment-resistant depression. By exploring both established and novel therapeutic avenues, this review underscores the evolving landscape of antidepressant pharmacotherapy and highlights future directions in neuropsychiatric treatment.

Keywords: Antidepressants, neuropharmacology, mechanisms, drug classes, therapy, mood disorders, neurotransmitters

Introduction
Depression is a prevalent and debilitating mental health disorder characterized by persistent sadness, loss of interest, and cognitive dysfunction. It is associated with significant morbidity and a high socioeconomic burden worldwide. Antidepressants remain the cornerstone of pharmacological treatment for depression, with their efficacy rooted in their ability to modulate neurotransmitter systems within the brain. Neuropharmacological, these agents primarily target monoaminergic pathways-particularly serotonin (5-HT), norepinephrine (NE), and dopamine (DA)-to restore chemical balance and improve mood and emotional regulation. Over the decades, the development of various classes of antidepressants, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and atypical agents, has broadened therapeutic options. Recent advancements in neurobiology have also shed light on the roles of neuroplasticity, neuroinflammation, and glutamatergic systems in depression, suggesting novel targets for next-generation antidepressants. This review aims to explore the neuropharmacological mechanisms of existing and emerging antidepressant therapies, offering insights into their clinical relevance and future directions.

Monoaminergic approaches
Monoamine oxidase inhibitors
Monoamine oxidase inhibitors (MAOIs) are a class of psychotropic drugs that act by inhibiting the monoamine oxidase enzyme, which is responsible for breaking down neurotransmitters such as serotonin, dopamine, and norepinephrine. By blocking this enzyme, MAOIs increase the availability of these neurotransmitters in the brain, leading to improved mood and mental function. They were among the earliest antidepressants developed and are particularly effective in treating atypical depression and treatment-resistant depression.

MAOIs are categorized based on their selectivity and reversibility. Irreversible non-selective MAOIs, such as phenelzine and tranylcypromine, inhibit both MAO-A and MAO-B enzymes permanently. Selective MAO-B inhibitors like selegiline and rasagiline are used in the management of Parkinson's disease due to their dopaminergic effects. Newer reversible inhibitors of MAO-A (RIMAs), such as moclobemide, offer therapeutic benefits with fewer dietary restrictions and a better safety profile compared to older MAOIs.

Despite their clinical efficacy, the use of MAOIs has declined due to their potential for serious side effects, including hypertensive crisis from interactions with tyramine-rich foods and serotonin syndrome when combined with other serotonergic drugs. However, recent developments such as transdermal formulations and more selective compounds have renewed interest in MAOIs for neuropsychiatric and neurodegenerative conditions. Ongoing research aims to improve their safety and expand their therapeutic applications.

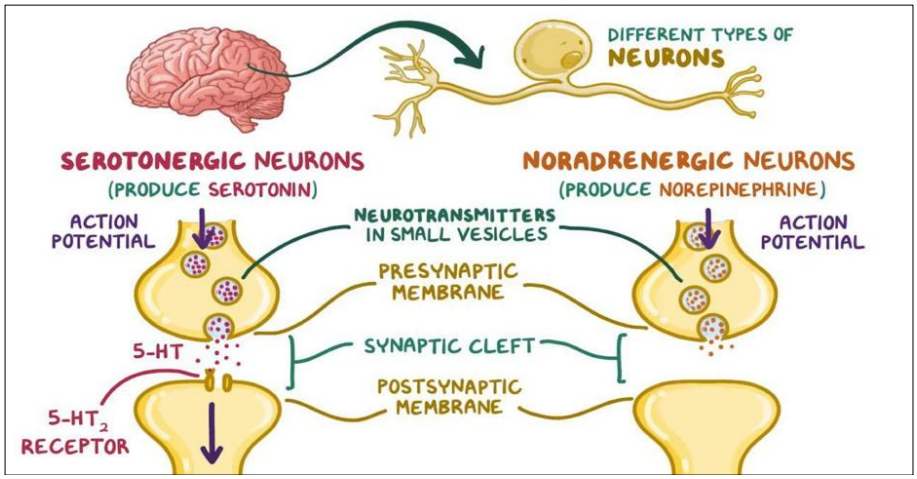


Table 1: Comparison of MAO Inhibitor Characteristics by Selectivity and Mechanism

Type	Example	MAO Isoform	Reversibility
Irreversible Non-selective	Phenelzine, Tranylcypromine	A & B	Irreversible
Irreversible Selective	Selegiline, Rasagiline	B	Irreversible
Reversible Selective	Moclobemide, Befloxatone	A	Reversible

Tricyclic antidepressants

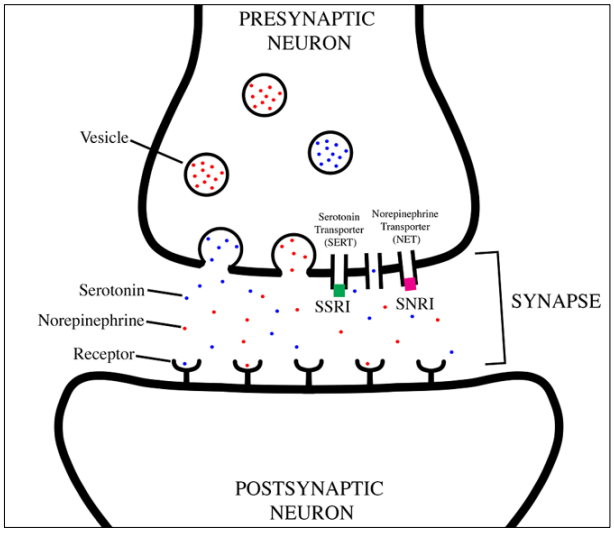
Tricyclic antidepressants (TCAs), named for their three-ring chemical structure (iminodibenzyl core), were the dominant class of antidepressants before the advent of SSRIs in the 1980s and 1990s. They exert their antidepressant effects primarily by inhibiting the reuptake of norepinephrine (NET) and serotonin (SERT), thereby enhancing synaptic concentrations of these neurotransmitters. Although they have minimal impact on dopamine (DAT) reuptake, TCAs are pharmacologically diverse and function as serotonin and norepinephrine reuptake inhibitors (SRI and NRI), as well as antagonists at muscarinic, histaminergic (H_1), and α_1-adrenergic receptors.

The TCAs used clinically include amitriptyline, imipramine, desipramine, nortriptyline, clomipramine, trimipramine, protriptyline, and doxepin. Despite subtle structural differences, these compounds vary significantly in their pharmacological profiles. For example, imipramine is a strong SRI with notable anticholinergic activity, while its metabolite desipramine is a more selective NRI with fewer anticholinergic effects. Clomipramine preferentially inhibits serotonin reuptake, making it effective in obsessive-compulsive disorder. TCAs essentially act as multi-target drugs, contributing to both therapeutic benefits and a broad side effect profile. The adverse effects of TCAs stem largely from their receptor-blocking activities. H_1 receptor blockade leads to sedation and weight gain, muscarinic receptor antagonism causes dry mouth, blurred vision, constipation, and cognitive dulling, while α_1-adrenergic blockade results in orthostatic hypotension and dizziness. At toxic doses, they can block sodium channels, posing a serious risk of cardiac arrhythmias and seizures. Today, TCAs are reserved for treatment-resistant depression or specific conditions like neuropathic pain, insomnia, and enuresis, due to their lower tolerability, complex titration, and high toxicity in overdose compared to newer antidepressants like SSRIs, SNRIs, and NASSAs.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective Serotonin Reuptake Inhibitors (SSRIs) are the most widely prescribed class of antidepressants due to their effectiveness, tolerability, and favorable safety profile. They function by selectively inhibiting the serotonin transporter (SERT), which is responsible for the reuptake of serotonin (5-HT) from the synaptic cleft back into the presynaptic neuron. By blocking this transporter, SSRIs increase the extracellular concentration of serotonin, enhancing serotonergic neurotransmission. This mechanism is thought to improve mood, emotional regulation, and other symptoms associated with depression and anxiety disorders.

Common SSRIs in clinical use include fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine. These agents are primarily used in the treatment of major depressive disorder, but also show efficacy in generalized anxiety disorder, panic disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and social anxiety disorder. They typically require 2-4 weeks to show clinical effects, and their ease of dosing and lower risk in overdose compared to tricyclic antidepressants (TCAs) have made them the first-line treatment in many psychiatric conditions.



Although generally well-tolerated, SSRIs are associated with side effects such as nausea, insomnia, sexual dysfunction, weight changes, and increased anxiety during initial treatment. In rare cases, they can lead to serotonin syndrome, especially when combined with other serotonergic agents. Additionally, abrupt discontinuation can cause withdrawal symptoms, known as SSRI discontinuation syndrome. Despite these limitations, SSRIs are preferred due to their high safety margin, minimal anticholinergic effects, and lower risk of cardiotoxicity, making them suitable for long-term use and for patients with coexisting medical conditions.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIS)

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) are a class of antidepressants that work by inhibiting the reuptake of two key neurotransmitters-serotonin (5-HT) and norepinephrine (NE)-through their respective transporters (SERT and NET). This dual mechanism enhances the levels of both neurotransmitters in the synaptic cleft, resulting in improved mood, emotional regulation, and pain modulation. By targeting both serotonergic and noradrenergic systems, SNRIs may offer therapeutic advantages over SSRIs in certain types of depression and pain-related disorders.

The most commonly prescribed SNRIs include venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran. These drugs are used to treat major depressive disorder (MDD), generalized anxiety disorder (GAD), social anxiety disorder, panic disorder, fibromyalgia, neuropathic pain, and chronic musculoskeletal pain. Duloxetine, in particular, is FDA-approved for multiple chronic pain conditions due to its balanced serotonin and norepinephrine activity. Venlafaxine is dose-dependent, acting more like an SSRI at lower doses and gaining significant norepinephrine reuptake inhibition at higher doses.

While SNRIs are generally well-tolerated, they can produce side effects such as nausea, dry mouth, dizziness, increased blood pressure (especially with venlafaxine), sweating, insomnia, and sexual dysfunction. Compared to TCAs, they have a better safety profile and fewer anticholinergic and cardiovascular side effects. However, abrupt discontinuation can lead to withdrawal symptoms, and blood pressure monitoring is advised in long-term use. Due to their efficacy in both mood and pain disorders, SNRIs are considered a valuable option for patients with depression accompanied by physical symptoms.

Atypical And Novel Antidepressants

Norepinephrine-Dopamine Reuptake Inhibitors (NDRIs)

Norepinephrine-Dopamine Reuptake Inhibitors (NDRIs) are a unique class of antidepressants that work by inhibiting the reuptake of norepinephrine (NE) and dopamine (DA), thereby increasing their availability in the brain and enhancing neurotransmission involved in mood, motivation, and energy. The primary and most well-known NDRI is bupropion, which is used for major depressive disorder (MDD), seasonal affective disorder (SAD), and as a smoking cessation aid. Unlike many other antidepressants, bupropion is not associated with sexual dysfunction or significant weight gain, making it a favourable option for patients concerned about these side effects. However, it can cause insomnia, dry mouth, anxiety, and in rare cases, seizures, especially at high doses or in individuals with predispositions. Due to its stimulating effects and favourable side effect profile, bupropion is often used as an adjunctive therapy alongside other antidepressants.

Serotonin Antagonist and Reuptake Inhibitors (SARIs)

Serotonin Antagonist and Reuptake Inhibitors (SARIs) are a class of antidepressants that combine serotonin reuptake inhibition with antagonism at specific serotonin receptors, primarily 5-HT_2A. This dual mechanism helps improve mood while also reducing anxiety, insomnia, and certain side effects commonly seen with SSRIs. The most commonly used SARIs include trazodone and nefazodone. Trazodone is frequently prescribed at lower doses for insomnia due to its strong sedative properties, while nefazodone has a more balanced antidepressant profile but is less commonly used because of rare cases of hepatotoxicity. SARIs tend to cause sedation, dizziness, dry mouth, and orthostatic hypotension, but they generally have a lower risk of sexual dysfunction compared to SSRIs. Their unique receptor activity makes them valuable options in patients with depression and sleep disturbances or as adjunctive treatments in combination therapies.

Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs)

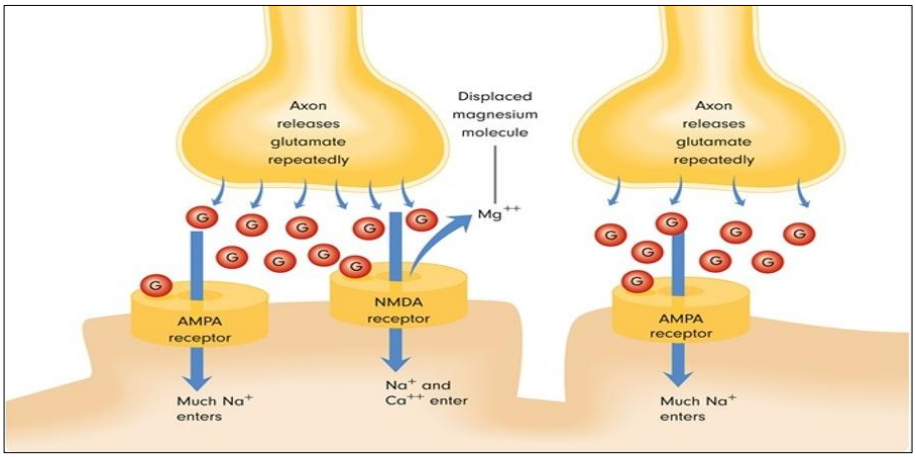
Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs) represent a distinct class of antidepressants that work by antagonizing central presynaptic α_2-adrenergic receptors, thereby enhancing the release of norepinephrine (NE) and serotonin (5-HT). Additionally, they block specific postsynaptic serotonin receptors, particularly 5-HT_2 and 5-HT_3, which contributes to their antidepressant and anxiolytic effects while minimizing typical serotonergic side effects. The main drug in this class is mirtazapine, which is used to treat major depressive disorder, especially in patients with insomnia, anxiety, or significant weight loss, due to its sedative and appetite-stimulating properties. Common side effects include increased appetite, weight gain, sedation, and dry mouth, but mirtazapine is notably less likely to cause sexual dysfunction or nausea compared to SSRIs and SNRIs, making it a suitable option for patients intolerant to those classes.

Recent Development in Anti-depressants drugs

Glutamate System and NMDA Antagonists

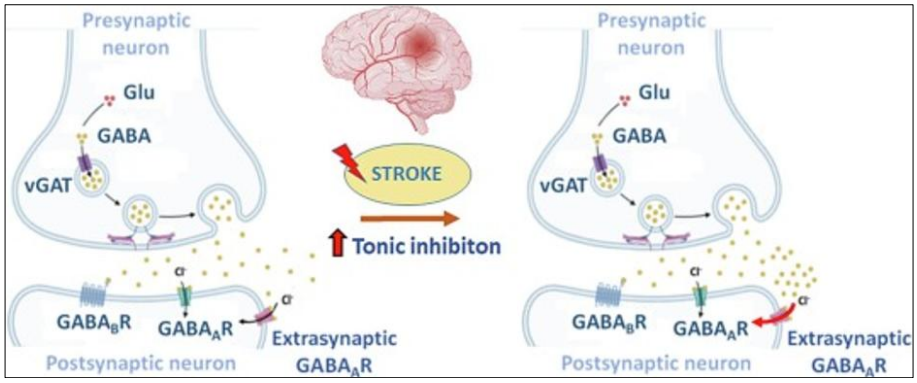
Glutamate system modulators, particularly NMDA (N-methyl-D-aspartate) receptor antagonists, represent a novel and rapidly evolving class of antidepressants targeting the

excitatory neurotransmitter glutamate, which plays a crucial role in synaptic plasticity, mood regulation, and neuroprotection. Unlike traditional monoaminergic antidepressants, NMDA antagonists offer rapid antidepressant effects, often within hours, making them promising for treatment-resistant depression (TRD) and suicidal ideation. The most prominent agent in this class is ketamine, a non-competitive NMDA receptor antagonist, and its S-enantiomer esketamine, which is FDA-approved as a nasal spray for TRD. These drugs modulate glutamatergic transmission, enhance AMPA receptor activity, and promote BDNF (brain-derived neurotrophic factor) signaling and synaptogenesis. Although effective, their use is limited by psychotomimetic effects, dissociation, and potential for abuse, requiring administration under controlled settings. Research is ongoing to develop safer glutamatergic agents with fewer side effects and longer-lasting benefits.



GABAergic Modulation

GABAergic modulation in depression therapy focuses on enhancing the activity of gamma-aminobutyric acid (GABA), the brain's primary inhibitory neurotransmitter, which is often dysregulated in mood disorders. Emerging research has shown that reduced GABAergic tone may contribute to depressive symptoms, anxiety, and impaired stress response. Agents targeting the GABA-A receptor, particularly positive allosteric modulators (PAMs) of specific subunits like the delta or alpha-5 subunits, offer promising antidepressant and anxiolytic effects without the sedative and addictive potential of traditional benzodiazepines. One notable example is brexanolone, an allosteric modulator of GABA-A receptors and a synthetic form of the neurosteroid allopregnanolone, approved for postpartum depression (PPD). GABAergic antidepressants represent a non-monoaminergic mechanism with rapid onset of action, and ongoing research aims to develop oral analogs with broader applicability in major depressive disorder and anxiety-related conditions.



Conclusion

The pharmacological operation of depression has significantly evolved from traditional monoaminergic medicines to the disquisition of new targets within the glutamatergic and GABAergic systems. While agents like SSRIs and SNRIs remain first- line curatives due to their safety and efficacity, newer medicines similar as ketamine and brexanolone offer rapid-fire relief in treatment- resistant cases, albeit with limitations regarding safety and administration. Understanding the multifaceted neurobiology of depression is essential to guide the development of further effective and more- permitted curatives. unborn antidepressant strategies should aim for individualized treatment, bettered onset of action, and minimum side goods by using advances in neuropharmacology, genetics, and molecular neuroscience.

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Conflicts of Interest

The authors declare no conflicts of interest. All of the authors have approved the final article.

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