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PHARMACODYNAMICS OF ANTIDEPRESSANTS AND THEIR NEW GENERATION (KETAMINE, ESKETAMINE)

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Annotation: This article examines the pharmacodynamic mechanisms of classical antidepressants and contrasts them with the emerging generation of rapid-acting agents, particularly ketamine and esketamine. Traditional antidepressants, including SSRIs, SNRIs, TCAs, and MAO inhibitors, primarily target monoaminergic neurotransmission and require several weeks before clinical benefits appear. Their limitations, combined with high rates of treatment resistance, have driven interest in novel approaches. Ketamine and esketamine represent a major shift in antidepressant development due to their rapid onset of action and unique effects on glutamatergic signaling, synaptic plasticity, and neurotrophic pathways. This article explores the cellular and molecular principles underlying their therapeutic properties, reviews clinical evidence, considers safety concerns, and outlines future research directions in neurobiologically informed treatments for major depressive disorder.

Keywords: antidepressants, pharmacodynamics, ketamine, esketamine, NMDA receptor, monoamines, neuroplasticity, treatment-resistant depression, glutamate modulation, synaptic connectivity

Major depressive disorder is a global health challenge, affecting hundreds of millions of individuals and contributing significantly to disability and mortality. For decades, pharmacological treatment has relied on agents that enhance monoaminergic activity, yet many patients fail to achieve remission. Even when effective, standard antidepressants require prolonged administration before meaningful improvements appear. This therapeutic gap has motivated the search for agents with novel mechanisms, faster action, and effectiveness in treatment-resistant cases.

Ketamine and esketamine represent the most significant advancement in antidepressant pharmacotherapy in more than half a century. Their discovery introduced a new neurobiological framework centered not on monoamines but on glutamatergic modulation and rapid restoration of synaptic integrity. Understanding their pharmacodynamics illuminates the broader shifts occurring in contemporary psychiatry.

This article analyzes both the established pharmacodynamics of conventional antidepressants and the innovative mechanisms underlying ketamine and esketamine, providing a comprehensive scientific overview of current therapeutic approaches.

Classical antidepressants emerged from the monoaminergic theory of depression, which proposes that deficits in serotonin, norepinephrine, or dopamine contribute to depressive

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symptoms. While this concept has guided treatment development for decades, it is now recognized as incomplete. Nevertheless, monoaminergic modulation remains the primary mechanism of most approved antidepressants.SSRIs inhibit reuptake of serotonin by blocking the SERT transporter, thereby increasing synaptic serotonin availability. Enhanced serotonergic signaling eventually leads to desensitization of inhibitory autoreceptors, normalization of neuronal firing, and changes in receptor expression. Therapeutic effects typically appear only after gradual neuroadaptive responses.

SNRIs block both SERT and NET transporters, increasing synaptic levels of serotonin and norepinephrine. The additional noradrenergic effect makes them particularly useful in patients with psychomotor slowing, fatigue, and comorbid pain syndromes. As with SSRIs, clinical effects depend on delayed intracellular adaptations.

TCAs inhibit monoamine reuptake but lack selectivity, also blocking histaminergic, muscarinic, and adrenergic receptors. This broad receptor activity accounts for both their efficacy and their considerable side-effect burden, including sedation, anticholinergic symptoms, weight gain, and cardiovascular toxicity.MAOIs prevent enzymatic breakdown of serotonin, norepinephrine, and dopamine by inhibiting monoamine oxidase. Although effective, especially in atypical depression, they require strict dietary restrictions and careful monitoring due to risks of hypertensive crisis and drug interactions.Ketamine is a non-competitive antagonist of NMDA receptors. At subanesthetic doses, it preferentially blocks NMDA receptors located on inhibitory interneurons. This temporarily reduces inhibitory control, resulting in increased glutamate release from pyramidal neurons.

The surge in glutamate stimulates AMPA receptors, an effect essential for ketamine's antidepressant properties. AMPA activation enhances excitatory neurotransmission and triggers synaptic strengthening.Ketamine increases brain-derived neurotrophic factor levels and activates the mTOR signaling pathway. These molecular events:

promote formation of new synapses

reverse stress-induced dendritic atrophy

restore functional connectivity in mood-related circuits

Such rapid synaptic changes explain ketamine's fast antidepressant onset.

Ketamine reduces levels of pro-inflammatory cytokines and modulates microglial activation. Given the recognized relationship between inflammation and depression, these effects may significantly contribute to therapeutic improvement.

Esketamine, the S-enantiomer of ketamine, has stronger affinity for the NMDA receptor and often produces clinical effects at lower doses. Administered intranasally, it provides a non-intravenous option for treatment-resistant depression and acute suicidal ideation. Its mechanism parallels ketamine but exhibits different pharmacokinetics and potency.

Conventional antidepressants require several weeks for therapeutic effects, while ketamine and esketamine can produce significant mood improvement within hours. This rapidity is clinically transformative, particularly for patients with severe symptoms or suicidal ideation.

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Traditional antidepressants indirectly facilitate neuroplasticity through long-term monoamine elevation. Ketamine directly triggers synaptogenic pathways, rapidly increasing synaptic density and functional connectivity.

Ketamine demonstrates unique efficacy against symptoms often resistant to conventional agents, such as:

anhedonia

emotional blunting

cognitive rigidity

suicidal thoughts

Ketamine and esketamine are particularly effective in individuals who do not respond to two or more standard antidepressants—one of the most significant advantages over older drug classes.Intravenous ketamine, usually administered at 0.5 mg/kg over 40 minutes, produces rapid improvement in treatment-resistant depression. Benefits often extend for several days, and repeated infusions may sustain remission. Ketamine may also improve cognitive flexibility and emotional responsiveness.

Esketamine offers a practical, outpatient-based treatment option. Used in combination with an oral antidepressant, it has demonstrated significant reductions in depressive symptoms in controlled trials. Its rapid action is particularly valuable in acute suicidal crises.Although initial responses are rapid, sustaining long-term remission may require maintenance dosing, psychotherapy integration, or adjunctive pharmacotherapy. Research continues to evaluate optimal long-term strategies.

psychotic disorders

uncontrolled hypertension

active substance abuse

Ongoing evaluation helps ensure safety and optimal outcomes.

The success of ketamine has catalyzed a new era of antidepressant development focused on glutamate modulation and neuroplasticity. Promising avenues include:

selective NMDA receptor modulators

AMPA receptor potentiators

neurotrophin-based therapies

compounds influencing synaptic scaffolding and connectivity

These emerging treatments aim to replicate ketamine’s benefits without dissociation or abuse potential.

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represents a profound transformation in the field of antidepressant therapy. While classical antidepressants rely heavily on monoaminergic modulation and require extended treatment periods, the new generation acts rapidly through glutamatergic pathways and direct enhancement of synaptic plasticity. Their ability to alleviate symptoms within hours, especially in treatment-resistant cases, has reshaped therapeutic strategies and broadened the conceptual framework for understanding depression.

Although further research is required to determine long-term safety and refine clinical protocols, ketamine and esketamine have opened the door to innovative treatments targeting the fundamental neurobiological disruptions underlying depressive disorders. Their introduction marks the beginning of a new chapter in psychopharmacology, where rapid correction of synaptic dysfunction promises more effective and timely relief for millions of patients worldwide.

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