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Advancing Treatment for Therapy-Resistant Depression: Insights from Animal Models

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Abstract

Treatment-resistant depression (TRD) remains a major clinical challenge, affecting a significant proportion of individuals diagnosed with major depressive disorder (MDD). Despite the availability of numerous antidepressant therapies, approximately one-third of patients fail to achieve remission after two or more adequate treatment trials. This review explores the critical role of animal models in understanding the neurobiological mechanisms underlying TRD and in developing more effective therapeutic strategies. Classical models such as the Forced Swim Test, Tail Suspension Test, and Learned Helplessness have provided foundational insights into depressive behaviors and antidepressant efficacy. However, these models often fall short in replicating the treatment-resistant phenotype. Emerging models such as those based on telomere dysfunction, genetic vulnerability, and comorbid anxiety-depression phenotypes offer promising platforms for investigating novel interventions. Additionally, the augmentation of pharmacological treatments, such as the co-administration of bupropion with SSRIs or SNRIs, highlights potential pathways for overcoming treatment resistance. The review emphasizes the importance of integrating behavioral, neurochemical, and genetic approaches to improve the translational validity of preclinical models. Ultimately, refining these models is essential for identifying effective and personalized treatments for individuals suffering from TRD.

Introduction

Major depressive disorder (MDD) is a leading cause of disability worldwide, with a lifetime prevalence of approximately 15% [1]. Although currently available antidepressants are effective for many individuals, a substantial proportion of patients fail to respond sufficiently. The STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial demonstrated that after two adequate and well-conducted antidepressant treatment trials, nearly one-third of patients do not achieve remission, meeting the criteria for treatment-resistant depression (TRD) [2]. Definitions of TRD vary, yet the most widely accepted criterion consists of persistent depressive symptoms following at least two antidepressant trials of adequate dose and duration. TRD is associated with severe functional impairment, elevated morbidity and mortality, and reduced quality of life [3]. Despite its high prevalence and societal burden, TRD remains insufficiently understood, and current treatment strategies typically involving antidepressant augmentation or combination yield limited efficacy. Preclinical models are essential for uncovering the neurobiological mechanisms driving TRD and for developing new therapeutics [4]. However, most classical depression models were not originally designed to capture treatment resistance and often oversimplify the complex neurobiology of chronic, refractory depression. This has fueled the growing consensus that new or adapted animal models are required to investigate TRD-specific mechanisms and identify more effective treatment strategies [5].

Classical Models of Depression

Classical animal models have been foundational in elucidating the neurobiological and pharmacological substrates of depressive behavior [6]. Although not developed to assess treatment resistance, they remain fundamental tools.

Behavioral Models of Depression

-The Forced Swim Test (FST) assesses behavioral despair based on the transition from active escape-oriented behaviors to immobility. Antidepressants consistently reduce immobility, making the FST a first-line screening tool for antidepressant efficacy [7].

-The Tail Suspension Test (TST) mirrors the FST conceptually but relies on tail suspension. It is sensitive to a broad range of antidepressants but can be influenced by strain, motor activity, and stress reactivity [8].

-The Learned Helplessness Model .Repeated exposure to uncontrollable stressors produces passive coping responses that resemble helplessness and anhedonia. This model is associated with alterations in motivation, reward processing, and neurochemical function [9], paralleling clinical depression more closely than acute tests.

Neurochemical and Neuroendocrine Dimensions of Depression

Classical models also reproduce alterations in neurotransmitter and hormonal systems implicated in MDD [10].

Serotonergic Dysregulation: Serotonin depletion models and serotonin transporter knockout mice highlight the role of serotonin deficiency in mood regulation and depressive-like behavior [11]. These insights align with the mechanism of SSRIs but also reveal why many patients—particularly those with inflammation-driven serotonin metabolism—may not respond.

Norepinephrine and Dopamine Systems: Disruptions in NE and DA neurotransmission contribute to anhedonia, psychomotor slowing, and cognitive deficits [12]. These findings underpin

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the rationale for using SNRIs or dopaminergic enhancers (e.g., bupropion) in TRD.

HPA Axis Dysregulation*:* Hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, manifested by elevated corticosterone/cortisol, is a well-characterized feature of stress-related psychopathology and depression [13]. High cortisol levels impair hippocampal neurogenesis, weaken synaptic plasticity, and contribute to antidepressant nonresponse—mechanisms now directly relevant to TRD.

Are There Models of Resistant Depression?

Because treatment resistance represents a more chronic, neuroprogressive, and biologically complex form of depression, researchers have developed adapted and novel models that capture this phenotype [14,15]. These include chronic stress paradigms, genetic selection models, inflammatory models, and models in which rodents fail to respond to typical antidepressants.

Mechanistic Insights into Pharmacological Treatments and Their Alignment with TRD Pathophysiology

Below is an expanded section integrating drug mechanisms with the biological abnormalities observed in TRD.

Ketamine and NMDA Receptor Antagonists: Ketamine has transformed TRD treatment owing to its rapid antidepressant effects [16]. Preclinical data confirm ketamine reduces immobility in FST and restores exploratory behaviors [17,18], paralleling clinical responses.

Mechanisms aligned with TRD pathophysiology

Synaptic plasticity restoration: Ketamine rapidly increases BDNF, activates TrkB receptors, and enhances synaptogenesis in PFC and hippocampus [19].

Glutamatergic normalization: TRD involves excessive glutamate, impaired NMDA signaling, and synaptic "noise." Ketamine restores excitatory–inhibitory balance.

mTOR pathway activation: TRD is associated with impaired mTOR signaling; ketamine rapidly activates mTORC1, increasing spine number and synaptic strength.

Anti-inflammatory effects: Ketamine reduces IL-6 and TNF-α and attenuates neuroinflammation, which is elevated in TRD.

Monoamine-independent action: Critical for TRD patients unresponsive to monoaminergic drugs.

Telomere Dysfunction and Lithium's Role

Telomeres shorten in depression, particularly chronic or stress-related forms, and shorter leukocyte telomeres predict poor antidepressant response [21]. The hippocampus—crucial for emotion regulation—is a major site of telomerase activity, yet telomere dysfunction has only recently been identified in depressive states [22].

In the Flinders Sensitive Line (FSL) rat, shortened telomeres, reduced telomerase activity, and low BDNF mimic the biological profile of TRD. Lithium restored telomerase activity, TERT expression, and β-catenin signaling [24].

Mechanistic alignment with TRD:

-Neuroplasticity enhancement (BDNF, β-catenin) counteracts hippocampal neurodegeneration.

-Cellular aging reversal, relevant as accelerated biological aging is consistently observed in TRD.

-Anti-inflammatory effects, reducing cytokines that impair treatment response.

-Lithium may therefore be uniquely positioned as a neuroprotective and proplasticity agent in TRD.

Ketamine, BDNF, and Neuroplasticity

Ketamine's robust induction of BDNF in the hippocampus [25] further supports its role in reversing structural and molecular abnormalities underlying TRD.

Genetic Models of Resistant Depression

Resigned (Selective Breeding) Mouse Lines

In these mice, depressive-like behavior is stable and resistant to multiple antidepressants [26]. They display:

reduced sucrose preference (anhedonia),

fragmented sleep,

reduced serotonin turnover,

exaggerated 5-HT1A autoreceptor sensitivity.

Fluoxetine normalizes some abnormalities but incompletely—modeling partial response.

Mechanistic relevance to TRD:

In humans, 5-HT1A autoreceptor overactivity predicts SSRI nonresponse.

Reduced serotonin turnover reflects monoamine-resistant depression.

Sleep fragmentation and HPA axis alterations mimic severe, chronic TRD.

Kynurenine Pathway Dysregulation

Altered kynurenine metabolism contributes to neuroinflammation and glutamatergic excitotoxicity [27,28]. TRD patients show increased quinolinic acid (NMDA agonist) and reduced kynurenic acid (NMDA antagonist).

Drug mechanism relevance:

Explains insufficient response to SSRIs in inflammation-driven depression.

Supports using ketamine, anti-inflammatory drugs, and glutamate modulators in TRD.

H/Rouen Mouse Model

These mice exhibit depressive- and anxiety-like phenotypes, as well as heightened cocaine CPP [29]. Activation of mood and reward circuits (cingulate cortex, accumbens, basolateral amygdala) and

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altered BDNF levels [30-31] reflect dysregulation seen in chronic, comorbid TRD.

Pharmacological Combination Strategies

Because TRD involves deficits in serotonin, noradrenaline, and dopamine, combining reuptake inhibitors targeting multiple systems may produce synergistic effects. Co-administration of bupropion + SSRI/SNRI enhances antidepressant-like responses in FST [32–34].

Mechanistic rationale:

-Bupropion: boosts dopamine and norepinephrine → counteracts anhedonia and amotivation.

-SSRIs/SNRIs: provide serotonergic stabilization.

-The combination overcomes "monoamine ceiling effects" of single agents.

Conclusion

The development of therapies for treatment-resistant depression (TRD) is an urgent priority. Classical models have provided insight into depressive mechanisms but fall short in capturing chronicity, neuroprogression, monoamine nonresponse, and plasticity deficits that characterize TRD. This has led to the emergence of specialized models incorporating genetic vulnerability, chronic stress, inflammatory activation, glutamatergic dysfunction, and telomere biology.

New insights into TRD pathophysiology reveal convergent abnormalities:

-impaired synaptic plasticity (low BDNF, mTOR dysfunction),

-HPA axis hyperactivity,

-glutamatergic dysregulation,

-neuroinflammation and kynurenine pathway shifts,

-accelerated cellular aging (telomere shortening),

-monoamine system insensitivity.

These abnormalities align with the mechanisms of emerging therapies such as ketamine, lithium, anti-inflammatory drugs, dopaminergic enhancers, glutamate modulators, and antidepressant combinations—making mechanistically-informed drug development increasingly feasible. Although no single animal model can fully reproduce TRD, integrating behavioral, molecular, genetic, and neuroinflammatory models provides a powerful platform for discovering and validating new treatments. Continued refinement of these models will be essential for developing interventions that restore neuroplasticity, reverse biological aging, modulate inflammation, and ultimately improve outcomes for individuals suffering from this debilitating condition.

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