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Review Paper

Modern Pharmacological Paradigms in the Treatment of Depression

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ABSTRACT

Depression constitutes a profound and persistent global health concern, contributing substantially to disability and diminished quality of life across populations. Conventional antidepressant therapies, primarily targeting monoaminergic neurotransmission pathways such as serotonin, norepinephrine, and dopamine, have demonstrated limited efficacy in achieving full remission, rapid symptom resolution, and sustained therapeutic outcomes. The suboptimal response rates and delayed onset of action associated with these agents underscore the urgent need for mechanistically distinct and clinically effective pharmacological interventions. Recent advances in neuropsychopharmacology have catalyzed the exploration of novel therapeutic targets that transcend the traditional monoamine hypothesis. Contemporary approaches emphasize the modulation of glutamatergic neurotransmission, particularly via N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine and esketamine, which exhibit rapid and robust antidepressant effects. Parallel developments in electrophysiological and magnetic brain stimulation modalities, including transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS), have offered non-pharmacological avenues for treatment-resistant depression. Moreover, the emerging roles of neuroinflammation, gut–brain axis dysregulation, and gamma-aminobutyric acid (GABA) imbalance have inspired investigations into anti-inflammatory agents, microbiota-targeted therapies, and GABAergic modulators as promising adjuncts. Psychedelic-assisted therapies, leveraging compounds such as psilocybin and dimethyltryptamine (DMT), have further expanded the therapeutic landscape through their modulation of neural connectivity and plasticity. This review synthesizes current literature on these innovative strategies, delineating their molecular mechanisms, clinical efficacy, safety profiles, and translational prospects. Collectively, these approaches represent a paradigm shift in the pharmacological management of depression, offering new insights to overcome the therapeutic limitations of conventional antidepressant regimens.

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INTRODUCTION

Depression represents a multifactorial and highly prevalent neuropsychiatric disorder that imposes a profound burden on global public health systems. It affects individuals irrespective of age, gender, or socio-cultural context, thereby exerting wide-ranging psychological, social, and economic consequences. The World Health Organization (WHO) classifies depression as one of the primary contributors to global disability and morbidity, emphasizing its significant role in diminishing quality of life and overall productivity. Current epidemiological data estimate that more than 280 million people worldwide are afflicted by depressive disorders, highlighting its extensive prevalence and the critical necessity for innovative, evidence-based preventive and therapeutic interventions to mitigate its global impact.[1]

The classical framework for understanding depression, anchored in the monoamine hypothesis, has served as the foundational paradigm guiding the evolution of antidepressant pharmacotherapy. This model postulates that aberrations in monoaminergic neurotransmission—particularly involving serotonin, norepinephrine, and dopamine—constitute the central neurobiological basis of depressive symptomatology. Deficient synaptic availability or impaired regulation of these neurotransmitters is proposed to contribute to the affective, cognitive, and somatic manifestations associated with depressive disorders.[2] The development of the earliest antidepressant agents in the 1960s was predominantly guided by the monoamine deficiency hypothesis, which posited that diminished levels of monoaminergic neurotransmitters constitute the principal neurochemical basis of major depressive disorder (MDD). This theoretical construct laid the foundation for the synthesis of first-generation antidepressants, notably monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). Subsequent advances in neuropsychopharmacological research delineated the critical involvement of serotonergic dysregulation in depressive pathophysiology, thereby catalysing the emergence of second-generation agents—selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs)—which remain the mainstay of contemporary first-line antidepressant therapy.[3]

Although a wide spectrum of antidepressant agents, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), are clinically available, a significant proportion of individuals diagnosed with major depressive disorder (MDD) exhibit suboptimal therapeutic response or fail to attain complete remission. Additionally, the inherent latency in the onset of antidepressant action, a hallmark of conventional monoaminergic therapies, constitutes a major clinical limitation, particularly in the effective management of acute depressive states and treatment-resistant cases.[4] In recent years, the identification of ketamine as a potent and rapid-acting antidepressant has revolutionized the therapeutic landscape of major depressive disorder (MDD), leading to the clinical approval of its intranasal enantiomer, esketamine. Esketamine demonstrates rapid symptomatic improvement, particularly in patients with treatment-resistant depression (TRD); however, its clinical utility is constrained by safety concerns, adverse effects, and the potential for misuse. Collectively, the limited efficacy, delayed response, and unfavorable safety profiles of existing pharmacotherapies underscore the persistent therapeutic gap in MDD management. The heterogeneity of depressive symptomatology

further complicates treatment, as each patient exhibits a distinct constellation of biological, psychological, and environmental factors influencing disease manifestation. The multifactorial and non-unitary nature of MDD suggests the involvement of diverse and overlapping pathophysiological pathways governing individual susceptibility and resilience to depressive disorders.[5,6] The majority of currently approved antidepressant agents exert their therapeutic efficacy predominantly through modulation of monoaminergic signaling pathways. Nonetheless, the suboptimal clinical response observed in a significant proportion of individuals with major depressive disorder (MDD) indicates the contribution of additional, yet insufficiently characterized, neurobiological mechanisms to its pathophysiology. Therefore, it is imperative to expand the pharmacological landscape beyond monoamine-centric paradigms to achieve improved therapeutic outcomes. Advancements in this direction would enable the implementation of personalized and mechanism-based treatment strategies, aligning pharmacotherapy with the distinct neurochemical, genetic, and pathophysiological determinants inherent to each patient's depressive phenotype.[7] Recognition of the existing therapeutic limitations, in conjunction with an enhanced understanding of the complex and multifactorial etiology of depression, has catalyzed growing scientific interest in the pursuit of novel therapeutic strategies. The pressing need to develop interventions that transcend the constraints of conventional antidepressant therapies while engaging alternative neurobiological pathways and molecular mechanisms underscores the critical importance of innovation in contemporary mental health research.

The present review consolidates recent advances in the understanding of natural compounds, biological signaling cascades, and receptor systems that constitute promising novel targets for improving therapeutic efficacy in major depressive disorder (MDD). Strategies aimed at optimizing treatment outcomes encompass the identification of emerging molecular targets, elucidation of additional mechanisms underlying currently employed antidepressant agents, and evaluation of synergistic or adjunctive pharmacological combinations capable of enhancing clinical responsiveness. Accordingly, this review provides a succinct overview of existing antidepressant modalities alongside a comprehensive analysis of newly identified molecular entities with substantial therapeutic promise. Collectively, these insights underscore innovative pharmacological directions that merit further investigation to advance the development of precision-guided and mechanism-based antidepressant interventions.

METHODOLOGY

A comprehensive preliminary scoping search was undertaken using the PubMed database to identify novel therapeutic strategies for the management of depression in human subjects over the past decade. Both unipolar and bipolar depressive disorders were included in the search framework. The initial query employed Medical Subject Headings (MeSH) terms "major depressive disorder" OR "bipolar disorder" in conjunction with the keyword "treatment" within the Title/Abstract fields. This search yielded a broad compilation of emerging therapeutic modalities. Subsequently, a refined and targeted search was conducted in PubMed using the MeSH combination "major depressive disorder" AND "X," wherein "X" denoted each treatment strategy previously identified. To ensure the inclusion of high-quality evidence, systematic review and meta-analysis filters were initially applied; in the absence of such

studies, randomized controlled trials (RCTs) or clinical trials were considered. All eligible studies were evaluated for their methodological rigor and for data pertaining to the efficacy and safety of novel interventions.

Given the exploratory nature of this investigation, a narrative review approach was adopted rather than a systematic one, with the objective of synthesizing and contextualizing the most relevant findings in the field. The final literature selection was restricted to English-language publications indexed in PubMed and assigned a PMID. Articles were curated based on their relevance to the three principal domains of this review: (1) pharmacological agents acting on specific receptor systems, (2) modulators of key biological or neurochemical pathways, and (3) natural products exhibiting demonstrable antidepressant potential.

TREATMENT MODALITIES

Pharmacologically Antidepressants

This section presents a chronological evaluation of clinically approved antidepressant agents, organized according to their developmental timeline and subsequent clinical implementation. Despite their indispensable role in the pharmacological management of major depressive disorder (MDD), these therapeutic agents exhibit notable constraints, including adverse drug reactions, challenges related to dosage and administration, delayed onset of antidepressant efficacy, and limited therapeutic response across heterogeneous patient cohorts. Consequently, this section delineates a comprehensive yet concise analysis of their clinical efficacy profiles, potential off-label therapeutic applications, and intrinsic pharmacological limitations in the context of MDD treatment.

Ketamine

In the past decade, the recognition of the rapid-onset antidepressant properties of subanesthetic ketamine administration has catalysed a paradigm shift from the traditional monoaminergic hypothesis toward the exploration of glutamatergic mechanisms in the neurobiology of depression. Emerging evidence increasingly implicates aberrant glutamatergic signalling as a pivotal contributor to the pathophysiology of depressive disorders. Glutamate, the predominant excitatory neurotransmitter in the central nervous system (CNS), is integral to numerous neurophysiological processes, including synaptic plasticity, cognitive processing, and memory consolidation. Among these, synaptic plasticity serves as a fundamental neurobiological mechanism underpinning cognitive stability, affective regulation, and adaptive neural circuitry remodelling associated with mood and emotional homeostasis[8]

Ketamine, a phencyclidine analogue, acts as a noncompetitive antagonist of the N-methyl-D-aspartate receptor (NMDAR) and was initially synthesized in the 1960s for use as a dissociative anesthetic agent. NMDARs are heterotetrameric ionotropic glutamatergic receptors that necessitate the simultaneous binding of the co-agonists glutamate and glycine to their respective recognition domains on the NR2 and NR1 subunits to achieve activation. Under physiological conditions, receptor activity is regulated by magnesium ions that exert voltage-dependent inhibition via occupation of the phencyclidine binding site within the receptor channel pore. The antagonistic pharmacodynamics of ketamine are primarily mediated through high-affinity interaction at this phencyclidine binding locus, in addition to its non-selective engagement with the NR2 (A–D) subunits, culminating in the suppression of excitatory glutamatergic

neurotransmission and downstream neuroplastic signaling.[9]

In clinical pharmacotherapy, ketamine is utilized for the treatment of depressive disorders through multiple routes of administration, including intravenous (IV), intramuscular (IM), and intranasal delivery. The conventional IV protocol generally employs a subanesthetic dose of approximately 0.5 mg/kg administered over a 30–40minute infusion period, under continuous hemodynamic and physiological monitoring encompassing blood pressure, heart rate, and core temperature. Ketamine may be prescribed either as a monotherapeutic intervention or as an adjunctive agent alongside established antidepressant regimen. In instances where the standard 0.5 mg/kg infusion fails to elicit a satisfactory therapeutic response, dosage escalation to 0.75 mg/kg or 1 mg/kg may be warranted, contingent upon individual pharmacodynamic tolerance, clinical response, and safety considerations.[10] Multiple randomized controlled trials (RCTs) have provided robust evidence supporting the efficacy of a single intravenous infusion of ketamine in alleviating symptoms of treatment-resistant depression (TRD) that have proven unresponsive to conventional antidepressant therapies.[11] A meta-analysis encompassing 36 randomized controlled trials (RCTs)—including nine studies evaluating esketamine and the remainder assessing racemic ketamine—demonstrated that treatment with either formulation was associated with significantly enhanced therapeutic outcomes compared to placebo. Specifically, ketamine administration was correlated with higher response rates [pooled rate ratio (RAR) = 2.14; 95% confidence interval (CI): 1.72–2.66; I^2 = 65%], increased remission rates (RAR = 1.64; 95% CI: 1.33–2.02; I^2 = 39%), and greater reductions in depressive symptom severity [Cohen's standardized mean difference (d) = –0.63; 95% CI: –0.80 to –0.45; I^2 = 78%]. Furthermore, no statistically significant association was observed between ketamine treatment and study discontinuation due to adverse events (RAR = 1.56; 95% CI: 1.00–2.45; I^2 < 1%) or in the overall incidence of adverse events per participant (RAR = 2.14; 95% CI: 0.82–5.60; I^2 = 62%) relative to placebo.[12] The therapeutic efficacy of ketamine in the management of depressive disorders within adolescent and geriatric populations remains insufficiently characterized. A systematic review encompassing 13 studies involving participants aged ≤18 years and ≥60 years reported that ketamine administration produced rapid-onset antidepressant effects, typically manifesting within a latency period of ≤2 weeks. Superior clinical outcomes were observed in protocols employing higher or repeated dosing regimens and in open-label study designs compared to blinded trials. However, significant methodological heterogeneity and overall low study quality substantially constrain the generalizability and interpretative strength of these findings.[13]

Ketamine comprises two optically active enantiomers, R-ketamine (arketamine) and S-ketamine (esketamine), each possessing intrinsic antidepressant efficacy. Despite arketamine exhibiting a relatively lower binding affinity for the N-methyl-D-aspartate receptor (NMDAR) compared to esketamine, preclinical studies have demonstrated its superior and more durable antidepressant effects. These preclinical observations have been corroborated by recent clinical trial data, which further substantiate the extended-duration therapeutic efficacy and potential clinical advantages of arketamine in the management of depressive disorders.[14,15]

In 2019, the United States Food and Drug Administration (FDA) granted approval for the

intranasal formulation of esketamine, the S-enantiomer of ketamine, for the treatment of adults diagnosed with treatment-resistant depression (TRD).[16] Its therapeutic effectiveness in treatment-resistant depression (TRD) has been validated through multiple short-term randomized controlled trials (RCTs).[17,18] A double-blind, randomized withdrawal study encompassing 297 adult participants diagnosed with treatment-resistant depression (TRD) who achieved remission or a clinically significant response following esketamine administration demonstrated that continued maintenance therapy with intranasal esketamine, administered concomitantly with oral antidepressants, markedly extended the time to depressive relapse relative to treatment with oral antidepressants combined with placebo. These findings provide robust evidence supporting the therapeutic superiority and sustained efficacy of the esketamine-augmented treatment paradigm in the long-term management of TRD.[19]

In the United States, the clinical use of intranasal esketamine is governed by a Risk Evaluation and Mitigation Strategy (REMS) program to ensure its safe and controlled administration. Under this regulatory framework, esketamine distribution is restricted to certified medical institutions authorized to provide treatment exclusively to registered and eligible patients. The medication is self-administered by the patient under direct clinical supervision, with continuous monitoring by trained healthcare personnel for a minimum of two hours post-administration to assess tolerability and manage potential adverse events. Esketamine is securely stored within the healthcare facility, with off-site removal or home use strictly prohibited. This controlled access program is instituted to safeguard patient welfare and to mitigate risks of misuse, abuse, or diversion. The recommended initial dose for treatment-resistant depression (TRD) is 56 mg—administered as 28 mg per nostril—on the first treatment day, followed by dose titration between 56 mg and 84 mg based on individual therapeutic response and pharmacodynamic tolerability. Treatment sessions are typically conducted biweekly during the induction phase to optimize efficacy and safety outcomes.[20,21]

A meta-analysis encompassing 24 randomized controlled trials (RCTs) with a total of 1,877 participants revealed that racemic ketamine exhibited superior therapeutic outcomes compared to esketamine. Specifically, racemic ketamine was associated with higher overall response rates (RAR = 3.01 vs. 1.38) and remission rates (RAR = 3.70 vs. 1.47), alongside a lower incidence of treatment discontinuation (RR = 0.76 vs. 1.37), indicating enhanced efficacy and tolerability relative to esketamine.[22]

Persistent safety concerns constrain the broad clinical utilization of esketamine, given its association with multiple adverse effects such as excessive sweating (hyperhidrosis), dissociative phenomena, urinary tract discomfort, and the onset or exacerbation of suicidal ideation.[23,24] Consequently, substantial research efforts are underway to elucidate the underlying mechanisms of action, aiming to develop novel and optimized therapeutic agents for major depressive disorder (MDD) that exhibit rapid onset, sustained efficacy, and a minimized risk of adverse effects and abuse potential. Among the proposed mechanisms is the modulation of the neuropeptide precursor VGF.[25] activation of the serotonin 1A (5-HT1A) receptor[26] stimulation of the brain-derived neurotrophic factor (BDNF) signaling pathway and enhancement of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) activity[27] and stimulation of the ventral CA3 subregion of the hippocampus.[28]

Commonly observed adverse events linked to ketamine administration in depressive disorder management include dissociative phenomena, perceptual distortions or hallucinatory experiences, cognitive impairment or disorientation, transient hypertensive and tachycardic responses, along with gastrointestinal manifestations such as nausea and emesis, and vestibular disturbances including dizziness.[29]

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) enhance the synaptic availability of serotonin (5-hydroxytryptamine; 5-HT), norepinephrine, and dopamine by inhibiting the catalytic activity of monoamine oxidase isoforms A (MAO-A) and B (MAO-B), thereby preventing their metabolic degradation. Iproniazid represents the pioneering MAOI employed in the pharmacological treatment of depressive disorders.[30] Iproniazid was initially developed as an antitubercular agent; however, its administration was subsequently found to elicit mood enhancement, central nervous system (CNS) stimulation, and elevated levels of serotonin (5-HT).[31] Clinical observations indicated that iproniazid produced therapeutic responses in approximately 25% to 75% of patients with major depressive disorder (MDD) and demonstrated notable efficacy in mitigating the symptoms associated with atypical depression.[32] However, the non-selective and irreversible inhibition of monoamine oxidase enzymes led to excessive accumulation of tyramine, subsequently predisposing patients to adverse effects such as hypertensive crises, hypotension, and hepatotoxicity.[33] To enhance the safety profile and therapeutic efficacy of MAOIs, selective and reversible inhibitors of monoamine oxidase A (RIMAs) were developed in the 1980s. Moclobemide, a prototypical RIMA, has been extensively utilized in the clinical management of major depressive disorder (MDD).[34]

Phenelzine, tranylcypromine, and isocarboxazid are additional first-generation monoamine oxidase inhibitors (MAOIs) that continue to be employed in the management of treatment-resistant depression (TRD)[35], often in combination with other antidepressant agents.[36,37] Patients receiving these agents are advised to adhere to dietary restrictions limiting tyramine consumption in order to mitigate the risk of hypertensive episodes.[38]

Recent investigations have explored the off-label application of MAOIs in the management of Parkinson's disease. Preclinical studies in animal models demonstrated that selegiline and rasagiline enhanced synaptic plasticity by restoring long-term potentiation[39] and reduced cortical dopamine turnover, indicating potential neuroprotective and neuromodulatory effects.[40] Enhanced motor performance was reported in patients, suggesting a favorable therapeutic potential.[41]

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) exert an effect on the catabolism of monoamine neurotransmitters. Their primary therapeutic action involves competitive antagonism of the presynaptic serotonin (5-HT) and norepinephrine transporter (NET) proteins, thereby inhibiting the neuronal reuptake of these neurotransmitters. This blockade results in an increased extracellular concentration of 5-HT and norepinephrine within the synaptic cleft, which subsequently triggers the downregulation and desensitization of their respective presynaptic autoreceptors. Furthermore, the inhibition of reuptake, coupled with the absence of significant postsynaptic enzymatic degradation (e.g., by Monoamine Oxidase or Catechol-O-Methyl Transferase in the

synaptic space), sustains this elevated synaptic monoamine concentration. This resultant pharmacological increase in synaptic 5-HT and norepinephrine is the hypothesized neurobiological correlate responsible for the observed therapeutic efficacy in mitigating the clinical manifestations of Major Depressive Disorder (MDD).[42]

Imipramine, clomipramine (CLO), and doxepin (DXP) were developed as part of the initial generation of tricyclic antidepressants (TCAs). While all these agents share a fundamental mechanism of action, their clinical utility varies. Specifically, the selection of one TCA over another often depends on the patient's presenting symptoms, as CLO demonstrates superior efficacy in the treatment of Major Depressive Disorder (MDD) when compared to imipramine.[43]

Tricyclic antidepressants (TCAs) are associated with a substantial profile of deleterious side effects (i.e., iatrogenic sequelae).[44,45] These adverse effects largely stem from the drugs' non-selective affinity for and antagonistic activity at several postsynaptic receptors, specifically the histaminergic, adrenergic, and muscarinic receptors.[46,47] This broad receptor blockade contributes to a spectrum of clinical manifestations, including somnolence, potential gestational complications, and severe cardiovascular aberrations, such as impaired cardiac conduction, dysrhythmias, and acute myocardial events.[48,49]

Selective Serotonin Reuptake Inhibitors

The 1960s marked a critical era of investigation into the etiology of Major Depressive Disorder (MDD)[50], where studies illuminated the potential role of the monoamine neurotransmitter, 5-hydroxytryptamine (5-HT), in its pathophysiology. This mechanistic insight established a core therapeutic principle: the pharmacological potentiation of postsynaptic 5-HT receptor stimulation through the inhibition of presynaptic 5-HT reuptake. This strategy served as the conceptual basis for the design and synthesis of the Selective Serotonin Reuptake Inhibitors (SSRIs). Fluoxetine achieved the distinction of being the first SSRI to obtain regulatory clearance from the Food and Drug Administration (FDA), initiating the development of subsequent SSRI compounds that exhibit a more favorable therapeutic index and adverse effect profile relative to predecessor antidepressants (e.g., TCAs). While SSRIs acutely enhance the extracellular concentration of 5-HT within the synaptic cleft, a notable latency of therapeutic response is observed, typically spanning 2 to 3 weeks before clinical benefit is realized.[51] Consequently, research into the comprehensive mechanism of antidepressant action has evolved past the classical model of simple synaptic monoamine augmentation to encompass cellular processes, such as the promotion of hippocampal neurogenesis.[52,53]

The Serotonin-Norepinephrine Reuptake Inhibitors exhibit a tolerability profile largely congruent with that of the, encompassing common adverse events such as fatigue, gastrointestinal hypomotility (constipation), and sleep-wake cycle disturbances (insomnia)[54]. Furthermore, usage has been implicated in the potential impairment of metabolic homeostasis, particularly manifesting as a heightened risk of hyperglycemia.[55,56]

Gamma-aminobutyric acid (GABA) modulators

Gamma-aminobutyric acid functions as the predominant inhibitory neurotransmitter within the Central Nervous System, a role crucial for homeostatic regulation of neuronal excitability. Evidence suggests that the GABAergic system is subject to pathophysiological alterations in

individuals diagnosed with depressive disorders. These systemic perturbations are hypothesized to mediate a functional imbalance in the reciprocal signaling dynamics between excitatory and inhibitory neurotransmission pathways within the neural circuitry.[57] Brexanolone, which is categorized as a neurosteroid, has emerged as a novel therapeutic agent under investigation for the management of depressive syndromes. Chemically, it is a structural analog of the endogenous compound allopregnanolone. The core of its pharmacodynamic mechanism involves acting as a positive allosteric modulator at the receptor complex. This action effectively potentiates the GABA-mediated inhibitory neurotransmission, thereby amplifying the influx of chloride ions and hyperpolarizing the neuron.[58]

In March 2019, brexanolone received a landmark designation as the inaugural pharmacological agent specifically granted Food and Drug Administration approval for the clinical indication of Postpartum Depression.The compound's dispensing is subject to rigorous control, being exclusively administered to patients within healthcare facilities under restricted distribution protocols. These constraints are necessitated by the requirement for continuous surveillance during the intravenous infusion process, ensuring strict adherence to a mandatory Risk Evaluation and Mitigation Strategy.[59]

Dysfunction or disequilibrium within the GABAergic system is postulated to be relevant to the pathophysiology of specific subpopulations of patients afflicted with Major Depressive Disorder. Given the widespread distribution of GABAergic neurons, their significant innervation and modulatory influence upon other key neurochemical systems, and the established correlation between GABAergic modulation and successful antidepressant efficacy, this system remains a pivotal area for translational research. Consequently, the specific pharmacological manipulation of the system is considered paramount for attaining the requisite antidepressant activity of prospective therapeutic agents developed for future clinical use.

Receptor-Targeting Compounds as Potential Antidepressant

A principal translational research strategy in the advancement of novel treatments for Major Depressive Disorder focuses on the pharmacological manipulation of specific receptor systems and receptor families that are implicated in the disease's underlying pathophysiology.

This forthcoming section serves to review extant preclinical and clinical datasets pertaining to compounds that function as modulators of discrete receptor classes for the alleviation of depressive symptomatology. The specific receptor families to be discussed represent targets that have been historically underrepresented in depression research but have recently demonstrated significant potential for novel therapeutic intervention.

Opioid Receptors

The delta, kappa, and mu opioid receptors constitute a family of endogenous G protein-coupled receptors characterized by widespread expression across the central and peripheral nervous systems. These receptors execute critical functions in the homeostasis of essential physiological processes, notably stress axis regulation, hedonic signaling (reward processing), and affective state (mood). Their activation is mediated by the binding of endogenous opioid peptides, including endorphins, enkephalins, dynorphins, and nociceptin/orphanin, which subsequently initiate diverse downstream effector

mechanisms. Consequently, the pharmacological manipulation of these opioid receptors, whether through selective or non-selective agonists or antagonists, represents a promising therapeutic strategy for generating antidepressant activity.

Buprenorphine exhibits a distinct receptor pharmacology, functioning as a partial agonist at the mu opioid receptor and concurrently as an antagonist at the delta and kappa opioid receptors. BUP is characterized by a high binding affinity for both the and sites, with a comparatively lower affinity for the DOR.[60]

The success of opioid receptor-targeting treatments in patients with Treatment-Resistant Depression suggests that these patients require therapeutic interventions acting on molecular targets unique from monoamines. Opioid receptors are heavily involved in regulating crucial functions, including stress response, reward processing, mood, and fundamental biological processes like inflammation. Due to this extensive involvement, it is anticipated that modulating this family of receptors will be efficacious for treating various psychiatric illnesses.[61] However, utilizing the opioid system for treatment presents major drawbacks: chronic usage carries a significant abuse potential, and patients may develop tolerance or suffer withdrawal symptoms. These inherent risks and challenges associated with the opioid system have likely served as a substantial impediment to the development of novel therapeutics in this area.

N-methyl-D-aspartate Receptors

Increased extracellular concentrations of the excitatory amino acid neurotransmitter, glutamate, are strongly correlated with the pathophysiology of Major Depressive Disorder. Upon binding, glutamate activates the N-methyl-D-aspartate receptor, thereby triggering neuronal depolarization.[62]A second critical component is the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, another class of ionotropic glutamatergic receptor. The membrane insertion density and conformational stability of are indispensable for robust synaptic transmission, and their agonism can confer antidepressant properties. While both preclinical and clinical investigations have extensively focused on antagonists for managing depressive syndromes, the subsequent discussion will specifically address non-ketamine-related potential therapeutic targets for MDD.[63]

Nitrous oxide, which functions as an NMDAR antagonist, possesses antidepressant qualities strikingly similar to those of ketamine. Mechanistically, research indicates that N2O works by activating neuronal nitric oxide synthase and facilitating the restitution of synaptic plasticity.[64] Preclinical studies in mice show that N2O exposure mitigates depressive-like behaviors, enhances the expression of BDNF (Brain-Derived Neurotrophic Factor), and increases the action potential firing frequency within the medial prefrontal cortex mPFC[65] neural circuit. Clinically, N2O has demonstrated a rapid antidepressant response and a high response rate in patients with Treatment-Resistant Depression TRD.[66] It also significantly reduced Hamilton Depression Rating Scale HDRS scores in MDD patients, leading to a high rate of clinical remission. However, despite this therapeutic promise, the clinical deployment of N2O is hampered by constraints, including an unfavorable adverse effect profile and the logistical challenge associated with its mandatory gaseous delivery methodology.[67]

NMDAR antagonists have shown the ability to produce rapid antidepressant effects in both preclinical studies and initial human clinical

evidence, though more extensive trials are still needed to fully confirm their efficacy. A particularly novel strategy involves selectively targeting the GluN2B subunit of the NMDAR. This approach offers a path for achieving fast-acting symptom reduction and could serve as an alternative to ketamine-derived medications, especially for patients experiencing suicidal ideation. Furthermore, investigating combinatorial therapy—pairing NMDAR antagonists with established drugs like SSRIs or SNRIs—could deliver immediate symptom relief from the NMDAR agent alongside the sustained antidepressant activity provided by the traditional monoaminergic drugs. Finally, other existing NMDAR antagonists, such as memantine and amantadine, require rigorous clinical investigation to determine their potential utility in treating Treatment-Resistant Depression TRD.

Peroxisome Proliferator-Activated Receptors

The Peroxisome Proliferator-Activated Receptors (PPARs) constitute a family of nuclear transcription factors instrumental in regulating fundamental physiological processes, including lipid catabolism, glucose flux homeostasis, overall bioenergetic equilibrium, and inflammatory responses. Evidence suggests a correlation between the downregulation of specific PPAR isoforms alpha, beta, delta, and gamma and the manifestation of depressive-like phenotypes. Given this association, the pharmacological manipulation of these receptors represents a significant area of therapeutic investigation for the management of depressive disorders.[68]

Given the Peroxisome Proliferator-Activated Receptors (PPARs) are involved in key neurobiological processes implicated in depressive states, notably neurogenesis and diverse cellular/behavioral plasticity mechanisms, their pharmacological modulation represents a significant therapeutic research frontier. Preclinical investigations have demonstrated that the co-administration of PPAR[69] agonists with established agents (either statins or Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)) results in a synergistic potentiation of the overall antidepressant activity, suggesting a critical mechanistic convergence underlying their therapeutic effect. Consequently, the dedicated drug development initiative focusing on novel PPAR agonists is strongly warranted. Furthermore, combinatorial clinical trials should prioritize exploring the therapeutic benefit in patients already undergoing treatment with SSRIs, SNRIs, or statins, as the addition of a PPAR agonist may significantly augment their existing regimen's efficacy.[70]

G-Protein-Coupled Receptor 39

The G protein-coupled receptor 39 (GPR39) is strongly implicated in the pathophysiology of Major Depressive Disorder (MDD).[71] Experimental gene silencing of GPR39 in murine models resulted in the manifestation of exacerbated anxiety-like and depressive-like phenotypes, heightened reliance on passive coping strategies, and induced treatment resistance to Monoamine Oxidase Inhibitors (MAOIs).[72] Conversely, evidence suggests that agonism of the GPR39 receptor confers significant antidepressant activity; for instance, the selective GPR39 agonist, TC-G 1008,[73] induced protracted antidepressant-like effects compared to the acute administration of reference compounds. Furthermore, Ghrelin, an endogenous GPR39 ligand and orexigenic peptide, has been shown in rodent models to attenuate neuroinflammation and mitigate depressive-like behaviors consequential to myocardial infarction (MI).[74] Collectively, these data nominate zinc (Zn2)[75] supplementation or the direct pharmacological targeting of Zn2 sensing

receptors as viable therapeutic avenues for MDD. However, Zn2 administration is associated with various adverse events (including pyrexia, emesis, dyspepsia, and dyspnea),[76] and because this symptom profile overlaps with the known side-effect burden of existing antidepressants, co-administration could lead to additive or synergistic adverse effects. Therefore, rigorous preclinical investigations are required to definitively elucidate the molecular mechanisms underlying these behavioral observations.

Galanin Receptors

Galanin is a neuropeptide widely distributed in Central Nervous System (CNS) neurons that interacts with three distinct galanin receptor (GALR) subtypes GALR1, GALR2, and GALR3, which can exist as either hetero- or homo-dimers. Functionally, GALR2 mediates excitatory signaling, whereas GALR1 and GALR3 facilitate inhibitory signaling. Therapeutically, GALR2 activation is associated with antidepressant effects, while activation of GALR1 and GALR3 is linked to an increase in depressive-like behaviors.[77,78]

Recent research aimed at uncovering the molecular mechanism by which these galanin receptors GALR influence depression has involved utilizing the synthesized galanin analog GAL (1–15). This analog is an active N-terminal fragment derived from the full galanin neuropeptide.[79]

Targeting Fundamental Biological Pathways for Depression

An alternative strategy for developing antidepressant treatments focuses on modulating broad biological pathways and processes rather than specific receptors. This approach aims to rectify the underlying dysregulated cellular and physiological effects associated with depression. In the following section, we will review biological processes known to be central to the development of depression, including inflammation, the Hypothalamic-Pituitary-Adrenal (HPA) axis, cholesterol biosynthesis, and gut microbiota. Our focus will be on reports demonstrating strong antidepressant potential within these novel areas.

Anti-inflammatory agents

The conceptual framework of depressive disorders has advanced beyond the classical monoamine hypothesis to encompass the involvement of the immune system, specifically the inflammatory cascade. A substantial and accumulating body of evidence indicates a complex bidirectional interplay between systemic inflammation and the pathogenesis of depressive syndromes. Individuals diagnosed with depression consistently exhibit upregulated systemic concentrations of key pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and C-reactive protein (CRP). These circulating inflammatory mediators are capable of traversing the blood-brain barrier, thereby initiating neuroinflammation and compromising crucial neuroregulatory homeostatic mechanisms. This subsequent neural disruption is theorized to underpin both the etiology and the chronicity of depressive symptomatology.[80]

Psychedelics

Psychedelic compounds possess an extensive historical record of application across diverse cultural contexts for sacramental, spiritual, and therapeutic practices; for example, psilocybin-containing fungi have held profound significance in indigenous rituals for millennia. Concurrently, synthetic compounds such as LSD (lysergic acid diethylamide) were developed during the mid-20th century. These agents were initially subjected to scientific inquiry for their putative therapeutic

efficacy before their widespread association with the 1960s countercultural phenomena led to their scientific marginalization. During this initial investigative phase, researchers explored the potential of psychedelics for numerous neuropsychiatric conditions, including Major Depressive Disorder. Preliminary studies indicated that psychedelics could facilitate subjective profound psychological experiences and enhance emotional processing/insight, suggesting considerable therapeutic utility. However, this promising research track experienced an abrupt cessation in the 1970s, primarily imposed by stringent regulatory constraints and pervasive sociocultural opposition.[81]

Over the last ten years, interest has surged in using psychedelics like psilocybin, MDMA (3,4-methylenedioxy-N-methylamphetamine), and LSD as promising tools in mental health care, particularly for treating depression. These compounds exert their primary effects by modulating serotonin receptors, most notably the 5-HT2A receptor. This receptor modulation leads to measurable neurobiological changes, including altered patterns of neural connectivity, increased neuroplasticity, and changes in the activity of the Default Mode Network (DMN). Scientists hypothesize that these specific neurobiological shifts are the foundation for the observed therapeutic effects of psychedelics in managing depression.[82]

A critical component of psychedelic research involves evaluating their safety and tolerability. While these substances are typically well-tolerated in clinical settings, it is vital to recognize potential risks. These risks include possibilities like acute psychological distress (a "bad trip"), the potential for dependence, and the exacerbation of pre-existing mental health conditions. To minimize these dangers, rigorous screening protocols and the use of supportive therapeutic settings are essential. Future investigations must prioritize standardizing treatment protocols, resolve various regulatory hurdles, and thoroughly examine the long-term effects and potential risks associated with psychedelic use.[83]

Table No.1: 💊 Novel Treatments for Depression: Evidence and FDA Status

Drug/ Treatment	Primary Mechanism of Action	🚦 FDA Status & Indication	✨ Evidence Base & Novelty
Brexanolone (Zulresso)	**Neurosteroid**; Positive Allosteric Modulator (PAM) of GABA-A receptors.	✅ **FDA Approved (2019)** for **Postpartum Depression (PPD)**.	First and only drug specifically approved for PPD. Known for its **rapid, acute symptom resolution**.
Esketamine (Spravato)	Non-competitive **NMDAR Antagonist** (targets Glutamate system).	✅ **FDA Approved (2019)** for **Treatment-Resistant Depression (TRD)** and acute suicidal ideation.	Delivers **rapid antidepressant effects** (within hours). Requires controlled, supervised administration.
Dextromethorphan/ Bupropion (Auvelity)	**NMDAR Antagonist** (DM) + NET/DMI Reuptake Inhibitor (Bupropion, enhances DM levels).	✅ **FDA Approved (2022)** for **Major Depressive Disorder (MDD)** in adults.	First oral, rapid-acting NMDAR antagonist combination approved for broad MDD use.
Psilocybin (Investigational)	**5-HT 2A Receptor Agonist** (Psychedelic).	🚫 **Not FDA Approved.** Schedule I substance.	Promising Phase 2/3 data for TRD. Being studied for **rapid, durable effects** from

			single/few doses combined with psychotherapy.
Buprenorphine/ Samidorphan (Investigational for MDD)	**Partial Agonist** (BUP) + **MOR Antagonist** (Samidorphan added for abuse mitigation).	⚠️ **Not FDA Approved for MDD** (Components approved for other uses).	Evidence of efficacy in TRD by modulating the opioid system while limiting addiction potential.
Nitrous Oxide (N2O) (Investigational)	Non-competitive **NMDAR Antagonist**.	🔎 **Not FDA Approved for Depression.**	Demonstrates **rapid, ketamine-like activity** in trials, but clinical implementation is hindered by inconvenient administration and adverse effect profile.

CONCLUSION

The synthesis of recent pharmaceutical approaches for depression, encompassing both synthetic molecular entities and natural products, aims to modulate either discrete receptor targets or pervasive biological signaling processes. Current antidepressant modalities are often deemed insufficient due to liabilities such as detrimental adverse effect profiles, a marked latency in therapeutic onset, and generally suboptimal efficacy. This inadequacy is partly attributable to an incomplete elucidation of MDD's etiology; since first-line agents predominantly address monoamine neurotransmission, it is empirically clear that the underlying molecular mechanisms of depression are multifactorial and transcend this single pathway. Consequently, future drug development must prioritize research aimed at defining the mechanisms of neurobiological resilience or susceptibility and the identification of associated genetic and epigenetic risk determinants. Recognizing MDD as a heterogeneous disease state, personalized pharmacotherapy becomes indispensable, where expanding the portfolio of available agents will enable clinicians to optimize treatment based on a patient's symptom cluster, risk factors, and history of prior treatment response. As more molecular modulators are functionally implicated in MDD's development, the strategy of combinatorial therapy—addressing multiple concurrent dysregulated pathways—warrants rigorous exploration. Regarding natural compounds (e.g., probiotics), suggestive evidence of antidepressant potential exists, yet definitive efficacy is limited by a critical deficit of large-scale, placebo-controlled, double-blinded clinical trials, which are essential for validating their therapeutic role and investigating their use in combination regimens. Finally, since a significant proportion of the novel targets described are in early-stage preclinical discovery, prioritizing research into these nascent mechanisms is crucial for their translational progression toward rigorous clinical studies, ultimately leading to the development of demonstrably improved treatment modalities.

REFERENCE

1. Depressive Disorder (depression). Geneva: WHO; c2024 [cited 2024 May 26].
2. Delgado PL. Depression: the case for a monoamine deficiency. J Clin Psychiatry. 2000; 61:7–11.
3. Shaw, D.M.; Camps, F.E.; Eccleston, E.G. 5-Hydroxytryptamine in the hind-brain of depressive suicides. Br. J. Psychiatry J. Ment. Sci. 1967, 113, 1407–1411.

4. Valenstein M. Keeping our eyes on STAR*D. Am J Psychiatry. 2006; 163:1484–6.
5. McEwen, B.S.; Akil, H. Revisiting the Stress Concept: Implications for Affective Disorders. J. Neurosci. 2020, 40, 12–21.
6. Torres-Berrío, A.; Morgunova, A.; Giroux, M.; Cuesta, S.; Nestler, E.J.; Flores, C. miR-218 in Adolescence Predicts and Mediates Vulnerability to Stress. Biol. Psychiatry 2021, 89, 911–919.
7. Fava, M. Diagnosis and definition of treatment-resistant depression. Biol. Psychiatry 2003, 53, 649–659.
8. Pal MM. Glutamate: The Master Neurotransmitter and Its Implications in Chronic Stress and Mood Disorders. Front Hum Neurosci. 2021; 15:722323
9. Lord, B.; Wintmolders, C.; Langlois, X.; Nguyen, L.; Lovenberg, T.; Bonaventure, P. Comparison of the ex vivo receptor occupancy profile of ketamine to several NMDA receptor antagonists in mouse hippocampus. Eur. J. Pharmacol. 2013, 715, 21–25.
10. Andrade C. Ketamine for Depression, 4: In What Dose, at What Rate, by What Route, for How Long, and at What Frequency? J Clin Psychiatry. 2017;78: e852–7
11. Jr CAZ, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006; 63:856–64.
12. Bahji A, Zarate CA, Vazquez GH. Efficacy and safety of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. Expert Opin Drug Saf. 2022; 21:853–66.
13. Vincenzo JDD, Siegel A, Lipsitz O, Ho R, Teopiz KM, Ng J, et al. The effectiveness, safety and tolerability of ketamine for depression in adolescents and older adults: A systematic review. J Psychiatr Res. 2021; 137:232–41.
14. Fukumoto, K.; Toki, H.; Iijima, M.; Hashihayata, T.; Yamaguchi, J.-I.; Hashimoto, K.; Chaki, S. Antidepressant Potential of (R)-Ketamine in Rodent Models: Comparison with (S)-Ketamine. J. Pharmacol. Exp. Ther. 2017, 361, 9–16.
15. Leal, G.C.; Bandeira, I.D.; Correia-Melo, F.S.; Telles, M.; Mello, R.P.; Vieira, F.; Lima, C.S.; Jesus-Nunes, A.P.; Guerreiro-Costa, L.N.F.; Marback, R.F.; et al. Intravenous arketamine for treatment-resistant depression: Open-label pilot study. Eur. Arch. Psychiatry Clin. Neurosci. 2021, 271, 577–582.
16. Kim J, Farchione T, Potter A, Chen Q, Temple R. Esketamine for Treatment-Resistant Depression - First FDA-Approved Antidepressant in a New Class. N Engl J Med. 2019; 381:1–4.
17. Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P, et al. Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. Focus (Am Psychiatr Publ). 2019; 17:55–65.
18. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2018; 75:139–48.
19. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2019; 76:893–903.

20. Kim J, Farchione T, Potter A, Chen Q, Temple R. Esketamine for Treatment-Resistant Depression - First FDA-Approved Antidepressant in a New Class. N Engl J Med. 2019; 381:1–4.
21. Spravato® (esketamine) nasal spray. Singapore: Janssen Global Services; c2012–2024 [cited 2024 May 26].
22. Bahji A, Vazquez GH, Jr CAZ. Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. J Affect Disord. 2021; 278:542–55. Erratum in: J Affect Disord. 2021; 281:1001.
23. Turner, E.H. Esketamine for treatment-resistant depression: Seven concerns about efficacy and FDA approval. Lancet Psychiatry 2019, 6, 977–979.
24. Kaur, U.; Pathak, B.K.; Singh, A.; Chakrabarti, S.S. Esketamine: A glimmer of hope in treatment-resistant depression. Eur. Arch. Psychiatry Clin. Neurosci. 2021, 271, 417–429.
25. Jiang, C.; Lin, W.-J.; Labonté, B.; Tamminga, C.A.; Turecki, G.; Nestler, E.J.; Russo, S.J.; Salton, S.R. VGF and its C-terminal peptide TLQP-62 in ventromedial prefrontal cortex regulate depression-related behaviors and the response to ketamine. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 2019, 44, 971–981.
26. Fukumoto, K.; Iijima, M.; Funakoshi, T.; Chaki, S. Role of 5-HT1A Receptor Stimulation in the Medial Prefrontal Cortex in the Sustained Antidepressant Effects of Ketamine. Int. J. Neuropsychopharmacol. 2018, 21, 371–381.
27. Agnieszka, P.-P.; Karolina, P.; Andrzej, P. Role of AMPA receptor stimulation and TrkB signaling in the antidepressant-like effect of ketamine co-administered with a group II mGlu receptor antagonist, LY341495, in the forced swim test in rats. Behav. Pharmacol. 2019, 30, 471–477.
28. Mastrodonato, A.; Martinez, R.; Pavlova, I.P.; LaGamma, C.T.; Brachman, R.A.; Robison, A.J.; Denny, C.A. Ventral CA3 Activation Mediates Prophylactic Ketamine Efficacy Against Stress-Induced Depressive-like Behavior. Biol. Psychiatry 2018, 84, 846–856.
29. Acevedo-Diaz EE, Cavanaugh GW, Greenstein D, Kraus C, Kadriu B, Zarate CA, et al. Comprehensive assessment of side effects associated with a single dose of ketamine in treatment-resistant depression. J Affect Disord. 2020; 263:568–75.
30. Pare, C.M.; Sandler, M. A clinical and biochemical study of a trial of iproniazid in the treatment of depression. J. Neurol. Neurosurg. Psychiatry 1959, 22, 247.
31. Marshall, E.F.; Stirling, G.S.; Tait, A.C.; Todrick, A. The effect of iproniazid and imipramine on the blood platelet 5-hydroxytrptamine level in man. Br. J. Pharmacol. Chemother. 1960, 15, 35–41.
32. West, E.D.; Dally, P.J. Effects of Iproniazid in Depressive Syndromes. Br. Med. J. 1959, 1, 1491–1494.
33. Davison, A.N. The mechanism of the irreversible inhibition of rat-liver monoamine oxidase by iproniazid (marsilid). Biochem. J. 1957, 67.
34. Bonnet, U. Moclobemide: Evolution, Pharmacodynamic, and Pharmacokinetic Properties. CNS Drug Rev. 2002, 8, 283–308.
35. Cusack, B.; Nelson, A.; Richelson, E. Binding of antidepressants to human brain receptors: Focus on newer generation compounds. Psychopharmacology 1994, 114, 559–565.
36. Owens, M.J.; Morgan, W.N.; Plott, S.J.; Nemeroff, C.B. Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. J. Pharmacol. Exp. Ther. 1997, 283, 1305–1322.

37. Aree, T. Supramolecular Complexes of β-Cyclodextrin with Clomipramine and Doxepin: Effect of the Ring Substituent and Component of Drugs on Their Inclusion Topologies and Structural Flexibilities. Pharmaceuticals 2020, 13, 278.
38. Ulrich, S.; Ricken, R.; Adli, M. Tranylcypromine in mind (Part I): Review of pharmacology. Eur. Neuropsychopharmacol. 2017, 27, 697–713.
39. Okano, M.; Takahata, K.; Sugimoto, J.; Muraoka, S. Selegiline Recovers Synaptic Plasticity in the Medial Prefrontal Cortex and Improves Corresponding Depression-Like Behavior in a Mouse Model of Parkinson's Disease. Front. Behav. Neurosci. 2019, 13, 176.
40. Ishikawa, T.; Okano, M.; Minami, A.; Tsunekawa, H.; Satoyoshi, H.; Tsukamoto, Y.; Takahata, K.; Muraoka, S. Selegiline ameliorates depression-like behaviors in rodents and modulates hippocampal dopaminergic transmission and synaptic plasticity. Behav. Brain Res. 2019, 359, 353–361.
41. Zhang, Z.; Shao, M.; Chen, S.; Liu, C.; Peng, R.; Li, Y.; Wang, J.; Zhu, S.; Qu, Q.; Zhang, X.; et al. Adjunct rasagiline to treat Parkinson's disease with motor fluctuations: A randomized, double-blind study in China. Transl. Neurodegener. 2018, 7, 14.
42. Schneider, J.; Patterson, M.; Jimenez, X.F. Beyond depression: Other uses for tricyclic antidepressants. Clevel. Clin. J. Med. 2019, 86, 807–814.
43. Montgomery, S.A.; Baldwin, D.S.; Blier, P.; Fineberg, N.A.; Kasper, S.; Lader, M.; Lam, R.W.; Lépine, J.-P.; Möller, H.-J.; Nutt, D.J.; et al. Which antidepressants have demonstrated superior efficacy? A review of the evidence. Int. Clin. Psychopharmacol. 2007, 22, 323–329.
44. Bye, C.; Clubley, M.; Peck, A.W. Drowsiness, impaired performance and tricyclic antidepressants drugs. Br. J. Clin. Pharmacol. 1978, 6, 155–162.
45. Kuenssberg, E.V.; Knox, J.D.E. Imipramine in Pregnancy. Br. Med. J. 1972, 2, 292.
46. Sloman, L. Myocardial infarction during imipramine treatment of depression. Can. Med. Assoc. J. 1960, 82, 20.
47. Freeman, J.W.; Mundy, G.R.; Beattie, R.R.; Ryan, C. Cardiac Abnormalities in Poisoning with Tricyclic Antidepressants. Br. Med. J. 1969, 2, 610–611.
48. ter Horst, P.G.J.; van der Linde, S.; Smit, J.P.; den Boon, J.; van Lingen, R.A.; Jansman, F.G.A.; De Jong-van den Berg, L.T.W.; Wilffert, B. Clomipramine concentration and withdrawal symptoms in 10 neonates. Br. J. Clin. Pharmacol. 2012, 73, 295–302.
49. Donoghue, J.; Tylee, A.; Wildgust, H. Cross sectional database analysis of antidepressant prescribing in general practice in the United Kingdom, 1993–5. BMJ 1996, 313, 861–862.
50. Shaw, D.M.; Camps, F.E.; Eccleston, E.G. 5-Hydroxytryptamine in the hind-brain of depressive suicides. Br. J. Psychiatry J. Ment. Sci. 1967, 113, 1407–1411.
51. National Collaborating Centre for Mental Health. Depression: The Treatment and Management of Depression in Adults (Updated Edition); British Psychological Society: Leicester, UK, 2010.
52. Malberg, J.E.; Eisch, A.J.; Nestler, E.J.; Duman, R.S. Chronic Antidepressant Treatment Increases Neurogenesis in Adult Rat Hippocampus. J. Neurosci. 2000, 20, 9104–9110.
53. Wang, J.-W.; David, D.J.; Monckton, J.E.; Battaglia, F.; Hen, R. Chronic fluoxetine stimulates maturation and synaptic plasticity of adult-born hippocampal granule cells. J.

Neurosci. Off. J. Soc. Neurosci. 2008, 28, 1374–1384.
54. Stahl, S.M.; Grady, M.M.; Moret, C.; Briley, M. SNRIs: Their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. CNS Spectr. 2005, 10, 732–747.
55. Fathallah, N.; Slim, R.; Larif, S.; Hmouda, H.; Salem, C.B. Drug-Induced Hyperglycaemia and Diabetes. Drug Saf. 2015, 38, 1153–1168.
56. Mekonnen, A.D.; Mills, A.A.; Wilhite, A.L.; Hoffman, T.K. Desvenlafaxine-associated hyperglycemia: A case report and literature review. Ment. Health Clin. 2020, 10, 85–89.
57. Cutler AJ, Mattingly GW, Maletic V. Understanding the mechanism of action and clinical effects of neuroactive steroids and GABAergic compounds in major depressive disorder. Transl Psychiatry. 2023; 13:228.
58. Edinoff AN, Odisho AS, Lewis K, Kaskas A, Hunt G, Cornett EM, et al. Brexanolone, a GABAA Modulator, in the Treatment of Postpartum Depression in Adults: A Comprehensive Review. Front Psychiatry. 2021; 12:699740.
59. Patatanian E, Nguyen DR. Brexanolone: A Novel Drug for the Treatment of Postpartum Depression. J Pharm Pract. 2022; 35:431–6.
60. Ramoz, N.; Hoertel, N.; Nobile, B.; Voegeli, G.; Nasr, A.; Le Strat, Y.; Courtet, P.; Gorwood, P. Corticotropin releasing hormone receptor CRHR1 gene is associated with tianeptine antidepressant response in a large sample of outpatients from real-life settings. Transl. Psychiatry 2020, 10, 378.
61. Morgan, M.M.; Christie, M.J. Analysis of opioid efficacy, tolerance, addiction and dependence from cell culture to human. Br. J. Pharmacol. 2011, 164, 1322–1334.
62. Casillas-Espinosa, P.M.; Powell, K.L.; O'Brien, T.J. Regulators of synaptic transmission: Roles in the pathogenesis and treatment of epilepsy. Epilepsia 2012, 53 (Suppl. 9), 41–58.
63. Koike, H.; Chaki, S. Requirement of AMPA receptor stimulation for the sustained antidepressant activity of ketamine and LY341495 during the forced swim test in rats. Behav. Brain Res. 2014, 271, 111–115.
64. Förstermann, U.; Sessa, W.C. Nitric oxide synthases: Regulation and function. Eur. Heart J. 2012, 33, 829–837.
65. Liu, W.; Li, Q.; Ye, B.; Cao, H.; Shen, F.; Xu, Z.; Du, W.; Guo, F.; Liu, J.; Li, T.; et al. Repeated Nitrous Oxide Exposure Exerts Antidepressant-Like Effects through Neuronal Nitric Oxide Synthase Activation in the Medial Prefrontal Cortex. Front. Psychiatry 2020, 11, 837.
66. Nagele, P.; Duma, A.; Kopec, M.; Gebara, M.A.; Parsoei, A.; Walker, M.; Janski, A.; Panagopoulos, V.N.; Cristancho, P.; Miller, J.P.; et al. Nitrous Oxide for Treatment-Resistant Major Depression: A Proof-of-Concept Trial. Biol. Psychiatry 2015, 78, 10–18.
67. Guimarães, M.C.; Guimarães, T.M.; Hallak, J.E.; Abrão, J.; Machado-de-Sousa, J.P. Nitrous oxide as an adjunctive therapy in major depressive disorder: A randomized controlled double-blind pilot trial. Braz. J. Psychiatry 2021.
68. Mirza, A.Z.; Althagafi, I.I.; Shamshad, H. Role of PPAR receptor in different diseases and their ligands: Physiological importance and clinical implications. Eur. J. Med. Chem. 2019, 166, 502–513.
69. Matrisciano, F.; Pinna, G. PPAR and functional foods: Rationale for natural neurosteroid-based interventions for postpartum depression. Neurobiol. Stress 2020, 12, 100222.
70. Beheshti, F.; Hosseini, M.; Hashemzehi, M.; Soukhtanloo, M.; Asghari, A. The effects of

PPAR-γ agonist pioglitazone on anxiety and depression-like behaviors in lipopolysaccharide injected rats. Toxin Rev. 2021, 40, 1223–1232.

71. Młyniec, K.; Nowak, G. Zinc deficiency induces behavioral alterations in the tail suspension test in mice. Effect of antidepressants. Pharmacol. Rep. 2012, 64, 249–255.
72. Młyniec, K.; Gaweł, M.; Nowak, G. Study of antidepressant drugs in GPR39 (zinc receptor−/−) knockout mice, showing no effect of conventional antidepressants, but effectiveness of NMDA antagonists. Behav. Brain Res. 2015, 287, 135–138.
73. Starowicz, G.; Jarosz, M.; Fr ˛ackiewicz, E.; Grzechnik, N.; Ostachowicz, B.; Nowak, G.; Mlyniec, K. Long-lasting antidepressant-like activity of the GPR39 zinc receptor agonist TC-G 1008. J. Affect. Disord. 2019, 245, 325–334.
74. Sun, N.; Mei, Y.; Hu, Z.; Xing, W.; Lv, K.; Hu, N.; Zhang, T.; Wang, D. Ghrelin attenuates depressive-like behavior, heart failure, and neuroinflammation in postmyocardial infarction rat model. Eur. J. Pharmacol. 2021, 901, 174096.
75. Wang, J.; Um, P.; Dickerman, B.A.; Liu, J. Zinc, Magnesium, Selenium and Depression: A Review of the Evidence, Potential Mechanisms and Implications. Nutrients 2018, 10, 584.
76. Staff, M.C. Zinc. Available online: https://www.mayoclinic.org/drugs-supplements-zinc/art-20366112 (accessed on 17 January 2022).
77. Bartfai, T.; Lu, X.; Badie-Mahdavi, H.; Barr, A.M.; Mazarati, A.; Hua, X.-Y.; Yaksh, T.; Haberhauer, G.; Ceide, S.C.; Trembleau, L.; et al. Galmic, a nonpeptide galanin receptor agonist, affects behaviors in seizure, pain, and forced-swim tests. Proc. Natl. Acad. Sci. USA 2004, 101, 10470–10475.
78. Morais, J.S.; Souza, M.M.; Campanha, T.M.N.; Muller, C.J.T.; Bittencourt, A.S.; Bortoli, V.C.; Schenberg, L.C.; Beijamini, V. Galanin subtype 1 and subtype 2 receptors mediate opposite anxiety-like effects in the rat dorsal raphe nucleus. Behav. Brain Res. 2016, 314, 125–133.
79. Millón, C.; Flores-Burgess, A.; Narváez, M.; Borroto-Escuela, D.O.; Santín, L.; Parrado, C.; Narváez, J.A.; Fuxe, K.; Díaz-Cabiale, Z. A Role for Galanin N-Terminal Fragment (1–15) in Anxiety- and Depression-Related Behaviors in Rats. Int. J. Neuropsychopharmacol. 2015, 18, pyu064.
80. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience. 2013; 246:199–229.
81. George DR, Hanson R, Wilkinson D, Garcia-Romeu A. Ancient Roots of Today's Emerging Renaissance in Psychedelic Medicine. Cult Med Psychiatry. 2022; 46:890–903.
82. Gattuso JJ, Perkins D, Ruffell S, Lawrence AJ, Hoyer D, Jacobson LH, et al. Default Mode Network Modulation by Psychedelics: A Systematic Review. Int J Neuropsychopharmacol. 2023; 26:155-88
83. Reiff CM, Richman EE, Nemeroff CB, Carpenter LL, Widge AS, Rodriguez CI, et al.; Work Group on Biomarkers and Novel Treatments; a Division of the American Psychiatric Association Council of Research. Psychedelics and Psychedelic-Assisted Psychotherapy. Focus (Am Psychiatr Publ). 2021;19: 95–115

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