

# ADVANCES IN TREATMENT OF MOOD DISORDERS

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### ABSTRACT

In recent years, there has been a shift in the focus of psychotropic research from traditional monoamine-based drugs to newer targets such as glutamate and GABA receptors. Ketamine has been investigated as an antagonist of N-methyl-D-aspartate (NMDA) receptors, leading to faster antidepressant responses compared to conventional treatments. Neuroactive steroids such as brexanolone and zuranolone have been found to effectively treat postpartum depression and major depressive disorder by modulating neuronal plasticity through enhancing Brain-derived neurotrophic factor (BDNF) levels. Researchers are exploring novel antidepressants that target the final common pathway of glutamate (NMDA/AMPA) and mTOR. Low doses of Lysergic acid (LSD) have been hypothesised to treat depression, social anxiety, and autism spectrum disorder. P2X7R, a channel involved in interleukin-1 $\beta$  production, can also be targeted to treat depressive symptoms. Reduced levels of brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), and insulin-like growth factor 1 (IGF-1) can lead to depressive symptoms, and antidepressants that enhance these levels can serve as novel treatments for depressive disorders. G-protein-coupled receptors (GPCRs) and neurotransmitters also play a significant role in the pathogenesis of depressive disorders. The glutamate hypothesis, which postulates that NMDA receptor antagonists exhibit antidepressant effects by enhancing the AMPA receptor's function, has been well-documented. Overall, the shift towards exploring new targets for psychotropic drugs has opened up new avenues for developing novel antidepressant treatments.

### KEYWORDS

Anti-depressive Agents, Ketamine, Neuro-steroids, Neurotransmitter Agents, Receptors, Treatment-Resistant Depressive Disorder

In the last several decades, psychotropics have mostly focused on Serotonin, Norepinephrine, and Dopamine for depression, and dopamine blockers for psychosis. Researchers started working diligently and explored new targets like Glutamate in treating depressive disorder and schizophrenia. The antagonist effect of Ketamine on N-methyl-D-aspartate (NMDA) receptors was investigated, which can result in a faster antidepressant response as compared to conventional treatment.<sup>1</sup> GABA receptors were also explored to develop novel compounds, which resulted in the discovery of brexanolone, a neuroactive steroid-positive allosteric modulator of GABA<sub>A</sub> ( $\gamma$ -Aminobutyric acid type A) approved in March 2019 by the FDA for the treatment of postpartum depression.<sup>2</sup> It is administered as an intravenous infusion over 60 hours and results in a rapid antidepressant response in postpartum depression lasting for more than one week.<sup>1</sup> Another neuroactive steroid, Zuranolone effectively treats postpartum depression and major depressive disorder (MDD).<sup>1</sup> The antidepressant also modulates neuronal plasticity by enhancing the Brain-derived neurotrophic factor (BDNF) levels.<sup>1</sup>

The researchers are now converging on a final common pathway, including glutamate (NMDA/AMPA) and mTOR, to develop novel antidepressants. The mTOR, known as the mechanistic target of rapamycin, is involved in cellular growth. The researchers are exploring the role of serotonin 5HT<sub>2</sub> receptors agonists, hypothesising that a low dose of Lysergic acid (LSD) can treat depression, social anxiety, and autism spectrum disorder. Antipsychotic drugs that do not target monoamine receptors are also discovered, including SEP-856, which is an agonist of the TAAR1 receptor (Trace amine receptor 1) and HT1A receptor antagonist.<sup>2</sup>

For half of the century, the monoamine hypothesis dominated the research regarding psychopharmacology based on the reduced availability of monoamine, particularly serotonin and noradrenaline, in the central nervous system.<sup>3</sup> The monoamine hypothesis does not fully explain the pathogenesis of depressive disorders, as conventional antidepressants are only effective in 60% of cases of Major depressive disorders (MDD).<sup>4</sup> The symptoms resolution is noticed mostly after two to three weeks of treatment, with a risk of adverse effects resulting in discontinuation.<sup>5</sup> The etiology of depressive disorders is multifactorial, including the hyperactivity of the hypothalamic-pituitary-adrenal (HPA axis). The HPA axis is regulated by the glucocorticoid receptors (GR), mineralocorticoid receptor (MR), and corticotrophin-releasing factor (CRF).<sup>6</sup>

The interleukin-1 $\beta$  plays an essential role in the pathogenesis of depressive symptoms and stress-related cellular activity.<sup>6</sup> P2X7R is an ATP-gated ion channel on the immune cells involved in the production of interleukin-1 $\beta$ .<sup>6</sup> Novel compounds targeting the P2X7R can treat depressive symptoms.<sup>7</sup> Decreased levels of brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), and insulin-like growth factor 1 (IGF-1) can also result in depressive symptoms.<sup>5</sup> The antidepressants that enhance the levels of these neurotrophic factors can be novel treatments for depressive disorders.

The role of G-protein-coupled receptors (GPCRs) and neurotransmitters is well known in the pathogenesis of depressive disorders.<sup>6</sup> GPCRs can be targeted for the development of novel antidepressant compounds.



The glutamate hypothesis originated in the 1990s when research established that N-methyl D-aspartate receptors (NMDA-R) antagonist has antidepressant properties. The amino acid glutamate is a major excitatory neurotransmitter, whereas GABA amino butyric acid (GABA) is an inhibitory neurotransmitter.<sup>1</sup> Glutamate plays a predominant role in memory, neuronal development, and synaptic plasticity.<sup>4,8</sup> It is estimated that 80% of the neurons in the neocortex are spiny and excitatory, whereas 20% are smooth and inhibitory.<sup>3</sup> The glutamate receptors are sub-characterized into ionotropic glutamate receptors, and G-protein coupled metabotropic glutamate receptors (mGluRs).<sup>6</sup> The ionotropic receptors include N-methyl-D-aspartate (NMDA),  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainite receptors.<sup>6</sup> Several studies have demonstrated that NMDA receptor antagonists can produce an antidepressant response, e.g., ketamine.<sup>6</sup> It is also postulated that NMDA receptor antagonists exhibit antidepressant effects by enhancing the AMPA receptor's function.<sup>4</sup>

The role of GABA receptors in depression has been demonstrated in various studies, opening new avenues to explore novel compounds.<sup>6</sup> Researchers have explored novel compounds that produce rapid antidepressant and anti-suicidal effects, including Ketamine in Treatment-Resistant Depression TRD. Ketamine is a chiral arylcyclohexylamine and is an NMDA receptor antagonist.<sup>12</sup> Ketamine has been used as an anesthetic agent since the 1960s, whereas its use in Treatment-Resistant depression was investigated in the early 2000s.<sup>3</sup> It interacts with GABA, serotonin, dopamine, cholinergic and opioid receptors.<sup>3</sup> Ketamine consists of a racemic mixture of two enantiomers, including (S) and (R) Ketamine, called esketamine and arketamine, respectively.<sup>9</sup> The esketamine has a three to fourfold higher affinity to NMDA receptors and is a potent anesthetic and analgesic.<sup>10</sup> The subanesthetic dose of Ketamine resulted in rapid antidepressant effects within hours compared to conventional antidepressants.<sup>9</sup> The antidepressant effect of Ketamine is mediated by the blockage of NMDA receptors on GABAergic interneurons; however, this results in a glutamate surge resulting in the activation of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which enhances neuroplasticity and synaptogenesis.<sup>10</sup> Ketamine enhances the BDNF levels and tropomyosin kinase B signaling (TrkB) along with the mammalian target of rapamycin complex<sup>1</sup> (mTORC1), contributing to its antidepressant effect by enhancing synaptic signaling proteins and spine density.<sup>10</sup> Ketamine is used in various forms, including intravenous, intranasal, oral, and intramuscular routes. The efficacy and safety of a single intravenous ketamine infusion have been established in various clinical trials.

The role of psychedelics has also been studied in treating psychiatric disorders. The psychedelics, including Lysergic acid diethylamide (LSD), psilocin, psilocybin (a prodrug of psilocin), and N, N-dimethyl tryptamine (DMT), interact with the serotonergic system, also called "classic serotonergic hallucination."<sup>11</sup> The psychedelic primarily acts as an agonist at 5HT<sub>2A</sub>. Preclinical studies have shown that psychedelics like LSD, psilocin, psilocybin, and DMT have improved depression-related behavior in rodents, primarily associative learning, which is a cognitive function impaired in MDD.<sup>11</sup> Psilocybin is 4-

phosphoryloxy-N, N-dimethyltryptamine has extensively been studied in treating depression, anxiety, and substance use disorder.<sup>12</sup> A meta-analysis established favorable outcomes regarding the use of psilocybin and behavioral intervention in treating depression and anxiety disorder, supporting future research in this area.<sup>12</sup> However, the phase 2 randomized control trial did not show a significant effect comparing psilocybin with escitalopram.<sup>13</sup>

NMDA receptors antagonist, including Dextromethorphan (DXM), Neudexta, dextromethorphan AVP786, and AXS-05 Axome, are nonselective, non-competitive and can be novel treatment modalities for depressive disorders.<sup>14</sup> DXM and its various enantiomers are considered potential novel compound for treating MDD. It is an NMDA receptor antagonist that affects serotonin and norepinephrine transporters, nicotinic and sigma-1 receptors. A review of the available data shows that DXM is well tolerated and has a significant antidepressant effect. Similarly, DXM in combination with bupropion was also studied and found safe and efficacious in treating MDD.<sup>15</sup> The safety and efficacy of DXM and bupropion are established in a phase 3 double-blind, placebo-controlled trial.

Similarly, a combination of buprenorphine with MOR antagonist samidorphan has been studied in an RCT in depression. Significant improvement in the Hamilton Depression Rating Scale (HAM-D) was observed along with a reduction in MADRS scores at the end of one week of treatment, with no withdrawal symptoms on stopping the medication.<sup>16</sup> Buprenorphine and samidorphan (ALKS-5461) were used in a dose of 2 mg/2mg as adjuvants, along with antidepressants in patients with MDD. This study showed significant improvement in the HAMD and MADRS scores.<sup>16</sup> ALKS-5461 was granted approval by FDA in October 2017 as fast-track-designated medicine. Later, the FDA drug advisory committee recommended further trials to establish the safety and efficacy of this compound. Other compounds under development using opioid receptor modulation include KOR antagonist JNJ-67953964, used for depression and substance use disorder.<sup>17</sup>

In summary, effective treatment strategies for mental illness are vital in dealing with this novel pandemic within the existing COVID-19 pandemic. The existing treatment for MDD and schizophrenia helps to some extent, but the dose does not provide a complete cure. The monoamine hypothesis, which has been the key to managing the depressive disorder, seems ineffective in Treatment-resistant depression. These limitations in the treatment of mood disorders have compelled researchers to explore novel compounds which have more efficacy with minimal treatment-emergent side effects. The concept of the bench to bedside in Psychopharmacology is a tedious process that includes significant background research for discovering novel compounds and enormous financial resources to establish their safety and efficacy in the patient population via clinical trials. The role of glutamate is revolutionizing the treatment of TRD, especially the use of Ketamine in providing a fast and effective antidepressant response compared to conventional treatment, along with its rapid anti-suicidal effects.



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