

Targeting the Glutamatergic System in Bipolar Disorder: A Review of Pharmacological Approaches

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Background: Bipolar disorder is a chronic mental disorder characterized by episodes of mania/hypomania and depression, with significant functional impairment and high global prevalence[1,2]. Although mood stabilizers and antipsychotics remain the standard treatment, their effectiveness is often limited by adverse effects and poor adherence[3,4]. Additionally, several conventional mood stabilizers exhibit a delayed onset of action, requiring up to three weeks, which reduces their usefulness in acute episodes. Therefore, glutamatergic agents, such as ketamine, have emerged as promising alternatives due to their rapid antidepressant effects and neuroprotective mechanisms[5,6]. **Objectives:** This study aimed at identifying pharmacological agents targeting the glutamatergic system and assess their efficacy. **Methods:** In this systematic review, a PIO strategy was used to identify articles analyzing the efficacy of glutamatergic agents in bipolar disorder. Searches were conducted in the databases ClinicalTrials.gov, PubMed and Web of Science. Eligible studies included phase II/III randomized clinical trials and controlled trials involving patients diagnosed with bipolar disorder. Methodological quality was assessed using the Joanna Briggs Institute (JBI) appraisal tool. Data were extracted into comparative tables including key information such as pharmacological agent, dosage, inclusion/exclusion criteria, study duration and main findings. **Results:** Thirteen articles were included in this study. Most trials were conducted in the United States of America (USA) (69%) and Taiwan (31%). USA studies primarily focused on ketamine, whereas Taiwanese studies investigated add-on memantine or dextromethorphan. Overall, glutamatergic modulators demonstrated promising effects in bipolar depression treatment, particularly ketamine, which was the most frequently studied agent. Ketamine stood out due to its rapid antidepressant effects. **Conclusions:** Glutamatergic modulators, especially ketamine, represent a promising approach for treatment-resistant bipolar depression, mainly because of their rapid antidepressant effect and their ability to reduce symptoms such as anhedonia and suicidal ideation. However, further studies are required to confirm the long-term efficacy and safety of these pharmaceuticals.

Keywords: Bipolar depression, Bipolar Disorder, NMDA, Glutamatergic modulators

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