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Sex Differences in Glutamate Pathologies: Implications in Ketamine Treatment for Depression and Alcohol Use Disorder

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Background: Major depressive disorder (MDD) and alcohol use disorder (AUD) are prevalent psychiatric conditions that are known to occur at different rates between men and women. Furthermore, both MDD and AUD are associated with different treatment outcomes between the sexes. Both MDD and AUD have been associated with glutamatergic dysregulation. Ketamine, an N-methyl d-aspartate glutamate receptor (NMDAR) antagonist, has shown preliminary efficacy in the treatment of MDD and alcohol use disorder (AUD). Numerous studies have shown differences in the regulation of the glutamate system between men and women, which suggests that there may be sex-dependent differences in response to ketamine treatment. The purpose of this review is to summarize the current knowledge of sex-specific outcomes of ketamine treatment for MDD and AUD. **Methods:** A search was conducted using the Scopus database to identify completed human and animal studies discussing the effectiveness of ketamine in the treatment of MDD and AUD between 1 January 1971 to 1 June 2020. **Results:** The results of the pre-clinical literature search suggest that there are differences between male and female animals' behavioral outcomes of ketamine treatment for depression and alcohol use disorder. However, the few human trials that have examined sex as a moderator of depression treatment response with ketamine have not found significant sex-based differences. Additionally, previous clinical trials of ketamine treatment for alcohol use disorder did not examine the sex-specific outcomes. **Conclusions:** While preclinical studies implicate sex as a moderator of treatment outcomes in MDD and AUD animal models, there have been few analyses in human trials of this potential confounder. Two of the three clinical trials have shown null findings, while one showed a small sex-based effect. Future studies should continue to evaluate sex-specific differences and should analyze the effects of female hormone levels on ketamine treatment outcomes.