The Need for Guidance on Ketamine/Esketamine Use in Real-World Clinical Settings

To the Editor: We read with great interest the recent article "Efficacy and Safety of Ketamine/Esketamine in Bipolar Depression in a Clinical Setting" by Santucci et al.[1] This study provides valuable insights into the real-world application of ketamine and esketamine for individuals with treatment-refractory bipolar depression, a condition associated with significant morbidity and an urgent need for effective interventions.

The findings are promising for the population with bipolar depression, where conventional treatments often show limited effectiveness, and the rate of treatment resistance is high. Moreover, they suggest that, at least in the short term, ketamine/esketamine treatments do not exacerbate manic symptoms, addressing a common concern among clinicians when considering these agents for bipolar patients. The reported occurrence of manic or hypomanic symptoms in nearly 29% of patients during the maintenance phase, with the frequency of these events averaging 1 event every 2.7 patient-years, appears relatively low, with only a single severe event resulting in hospitalization.

The authors state that there are no studies on esketamine augmentation in bipolar depression, but there is a study by Martinotti et al[2] of 35 subjects with treatment-resistant bipolar depression and 35 with unipolar treatment-resistant depression (TRD) treated with esketamine nasal spray (ESK-NS). The authors observed a stronger antidepressant and anxiolytic effect of ESK-NS among bipolar TRD subjects. They suggested that ESK-NS and other glutamatergic agents may be primary options for treating bipolar disorder. Some even suggest that ketamine/esketamine may have mood-stabilizing properties.[3]

Available data suggest that the risk of hypomanic/manic switching is low and does not exceed the potential benefits, which might be even more pronounced in bipolar patients (Wilkowska and Cubała[4]). The European Medicines Agency (EMA) Summary of Product Characteristics (SPCs) for ESK-NS does not contraindicate its use among patients with bipolar disorder, suggesting a careful evaluation of the risks and benefits of its application in this condition.[4]

As highlighted in this study, the importance of real-world evidence cannot be overstated. In many countries, esketamine remains costly and limited in availability, making racemic ketamine a more accessible alternative despite its off-label status. Real-world data, such as those presented by Santucci et al,[1] play a pivotal role in developing clinical guidelines that could enable the safe and effective implementation of racemic ketamine. Such guidelines would allow for broader access to a potentially life-saving treatment for patients with TRD and bipolar depression, especially where access to esketamine is constrained. A clinicians' guidance for the treatment of depressive disorders with racemic ketamine was recently developed in Poland with practicalities of the ketamine use per local standard of care. With all of its limitations in mind, it provides a valid educational activity that fits specific patient pathway, treatment setting, and specificity of the "off-label" drug use. This standard emphasizes careful patient selection, monitoring for adverse effects, and adherence to recommended dosing protocols to ensure both efficacy and safety in clinical practice.[5]

Overall, Santucci and colleagues' study contributes to a growing body of evidence on the utility of ketamine/esketamine in treating bipolar depression, with implications for both safety and efficacy in real-world clinical practice. As clinicians, we must continue to weigh the potential benefits of these treatments against the risks, especially when considering maintenance therapy.

References

1. Santucci MC, Ansari M, Nikayin S, et al. Efficacy and safety of ketamine/esketamine in bipolar depression in a clinical setting. *J Clin Psychiatry*. 2024;85(4): 24m15376.
2. Martinotti G, Dell'Osso B, Di Lorenzo G, et al. Treating bipolar depression with esketamine: safety and effectiveness data from a naturalistic multicentric study on esketamine in bipolar versus unipolar treatment-resistant depression. *Bipolar Disord*. 2023; 25(3):233–244.
3. d'Andrea G, Pettorruso M, Lorenzo GD, et al. Rethinking ketamine and esketamine action: are they antidepressants with mood-stabilizing properties? *Eur Neuropsychopharmacol*. 2023;70:49–55.
4. Wilkowska A, Cubała WJ. Short-term ketamine use in bipolar depression: a review of the evidence for short-term treatment management. *Front Psychiatry*. 2023; 14:1322752.
5. Gałecki P, Bliźniewska-Kowalska KM, Cubała WJ, et al. Polish standard of treatment with racemic ketamine for patients with depressive disorders developed by a Working Group appointed by the National Consultant in the field of psychiatry. *Psychiatr Pol*. 2024;58(3): 377–401.

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