



Esketamine for Postoperative Depressive Symptoms: Considerations for Broader Perioperative Practice [Response to Letter]

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Dear editor

We extend our sincere gratitude to Dr Matthewson for his thoughtful attention to our work and his valuable insights.¹ We have thoroughly examined each of his comments, which are highly constructive and precisely address the critical aspects of our research. These suggestions have significantly enhanced our understanding of the study's limitations and provided profound inspiration for future directions. Below, we provide a point-by-point response to the issues he raised.

Regarding the use of esketamine in treating perioperative depression, multiple studies involving diverse patient populations have been published to date, showing heterogeneous findings. A recent meta-analysis demonstrated that intravenous administration of esketamine is effective in alleviating postoperative depression in patients undergoing various types of surgery.² However, as noted by Dr Matthewson, psychological characteristics vary significantly across different populations. Although our study has shown promising results, whether esketamine exerts consistent benefits on postoperative emotional disorders in all patient subtypes remains a question worthy of further investigation.

We greatly appreciate Dr Matthewson's highly insightful comment regarding the potential role of analgesic effects as a mediating variable in mood improvement. His perspective is profound and opens new avenues for understanding the complex mechanism of action of esketamine.

We fully acknowledge the scientific plausibility of this mechanistic hypothesis. However, as the primary endpoints and design of our study were focused on assessing postoperative emotional outcomes, although pain-related data were recorded, systematic and high-frequency monitoring of opioid consumption was not performed. Consequently, rigorous subgroup or mediation analyses are currently infeasible. We acknowledge this as a limitation of our study.

We strongly agree that elucidating the respective contributions of direct antidepressant versus indirect analgesic effects represents a critical direction for future research. Subsequent studies should systematically collect pain and opioid use data and employ statistical methods such as mediation and stratification analyses to validate this hypothesis.

Regarding the limitation of the 30-day follow-up period, we fully concur with Dr Matthewson's point, as was also discussed in the Limitations section of our article. The onset and progression of depressive symptoms involve substantial complexity. Some patients may experience new-onset depressive symptoms or persistence of pre-existing symptoms beyond the first month after surgery, potentially due to delayed stress responses to surgical trauma or pressures during recovery. A 30-day follow-up could indeed miss these late-emerging cases.

In light of this issue, it would be essential to conduct a future prospective study with a refined design and extended follow-up—spanning 3 months, 6 months, or even longer. Such a study would not only help verify the durability of the treatment effect but also allow systematic evaluation of the intervention's impact on cognitive functions (such as long-term memory and

executive function) and overall social functional recovery. This is crucial for a comprehensive assessment of the clinical value of esketamine in the rehabilitation of breast cancer patients.

We fully acknowledge that the use of esketamine infusion requires careful monitoring for adverse effects such as dissociation and hemodynamic changes, and may pose resource challenges in some clinical settings. In our study, these events were generally mild and manageable with dose adjustment. Future implementation studies should indeed evaluate the cost-effectiveness, workflow integration, and safety protocols required for wider adoption across different perioperative environments.

We once again express our sincere gratitude to Dr Matthewson for his insightful and encouraging feedback. His comments have not only enriched the discussion of our current findings but will also inform the design of our subsequent investigations. We look forward to continuing to contribute meaningfully to this important field of perioperative medicine.

Disclosure

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References

1. Matthewson L. Esketamine for postoperative depressive symptoms: considerations for broader perioperative practice. *Drug Des Devel Ther.* 2025;19:10011–10012. doi:10.2147/DDDT.S578076
2. Huang C, Hu L, Liu W, et al. Efficacy and safety of esketamine on major depression, postpartum depression and perioperative depression: a systematic review and meta-analysis. *Mol Psychiatry.* 2025;1–4. doi:10.1038/s41380-025-03320-6

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