

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

Louise Matthewson

Imperial College Healthcare NHS Foundation Trust, London, UK

Correspondence: Louise Matthewson, Imperial College Healthcare NHS Foundation Trust, London, UK, Email [louise.matthewson1@nhs.net](mailto:louise.matthewson1@nhs.net)

## Dear editor

I read with great interest the recent randomised double-blind trial by Shen et al<sup>1</sup> evaluating the perioperative use of continuous esketamine infusion to reduce postoperative depressive symptoms in patients undergoing unilateral modified radical mastectomy through a double-blind randomised controlled trial (Registration No. ChiCTR2200061575, <https://www.chictr.org.cn/showproj.html?proj=172370>). The authors should be commended for addressing the important intersection between perioperative anaesthesia practice and mental health outcomes in a vulnerable patient population.

The study contributes valuable insight into the anxiolytic and antidepressant potential of esketamine in the perioperative period. However, several considerations merit further discussion to contextualise the findings and guide future research.

First, the exclusive inclusion of female breast cancer patients limits the generalisability of the results to broader surgical cohorts. Psychological vulnerability, perioperative stress response, and pain processing may differ across genders, cancer types, and surgical complexity. Future studies including male patients and non-oncological procedures would strengthen external validity.

Second, while the significant reduction in depressive symptoms at 30 days is encouraging, the mechanisms remain incompletely clarified. Although perioperative BDNF and 5-HT changes were reported, these biomarkers alone may not adequately reflect the complex neurobiological pathways implicated in perioperative mood disturbance. Incorporating additional inflammatory and neuroendocrine markers, alongside psychological screening tools, may provide a more comprehensive mechanistic understanding.

Third, esketamine's multimodal properties raise the possibility that improved early postoperative analgesia and reduced opioid consumption may have mediated mood benefits, rather than direct antidepressant effects alone. Stratified analyses examining pain scores, opioid use, and mood outcomes would help disentangle these interactions.

Additionally, the 30-day follow-up interval, whilst clinically meaningful, may not capture late emergence of depressive symptoms, which can persist or develop beyond the first postoperative month. Extended follow-up and assessment of cognitive and functional outcomes would provide important insight into sustained benefit and safety.

Lastly, while the anaesthetic community welcomes potential strategies to optimise psychological wellbeing around surgery, practical considerations remain. Esketamine infusion requires vigilance for haemodynamic effects, dissociation, and perioperative resource demand. Future research should also consider cost-effectiveness and feasibility across diverse perioperative settings.

In conclusion, this promising study advances the conversation around perioperative mental health, multimodal anaesthesia, and recovery pathways. Further multicentre trials with broader populations, longer follow-up, and mechanistic exploration will be invaluable in determining whether esketamine should be incorporated into routine perioperative practice for mood-related outcomes.

Thank you for the opportunity to comment on this important work.

## Disclosure

The author reports no conflicts of interest in this communication.

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## Reference

1. Shen M, Xuan Y, Chen K, et al. Effects of continuous perioperative esketamine infusion on postoperative depression in breast cancer patients: a randomized controlled double-blind trial. *Drug Des Devel Ther.* 2025;19:9685–9695. doi:10.2147/DDDT.S540781

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<https://doi.org/10.2147/DDDT.S578076>