European Archives of Psychiatry and Clinical Neuroscience
https://doi.org/10.1007/s00406-024-01810-2

EDITORIAL

Beneficial and adverse effects of ketamine and its enantiomers, and the underlying mechanisms of ECT and rTMS efficacy

Kenji Hashimoto[1]

Suicide represents a major global public health challenge, with a notably higher prevalence observed among individuals suffering from major depressive disorder (MDD) in comparison to the general population. Depression, widely recognized as a prevalent mental health disorder, is characterized by enduring sadness, diminished interest in activities, and a range of emotional and physical issues, all of which markedly elevate the risk of suicide. Recent meta-analysis findings have indicated that the severity of hopelessness is a significant predictor of suicidal ideation (SI) and suicide attempts [1]. Additionally, factors such as a history of suicide attempts, SI, severe depression, and psychotic symptoms have been identified as predictors of subsequent suicide attempts and suicide deaths [1]. In this issue, a scoping review by Phalen et al. [2] explores the notion that emotional distress and dysregulation could serve as promising therapeutic targets for addressing suicide in individuals with psychosis. Overall, the urgent need for the development of effective depression treatments remains a critical gap in the effort to prevent suicide.

Ketamine and its enantiomers have been shown to alleviate depressive symptoms and SI in severe patients with MDD, including those with treatment-resistant depression (TRD) [3, 4]. However, the impact of melancholic features on the anti-suicidal efficacy of ketamine infusion in TRD patients with significant SI has remained ambiguous. In this issue, Chen and colleague [5] observed that low-doses of ketamine produced rapid and sustained anti-suicidal effects in TRD patients with SI but lacking melancholic features, unlike those who exhibited such features. The anti-suicidal benefits of a single ketamine infusion lasted up to 5 days, as evaluated by clinicians, and up to 7 days based on patient self-reports. Nevertheless, TRD patients with SI and melancholic features might still experience some anti-SI benefits from ketamine. Further research is necessary to elucidate the influence of melancholic features on ketamine's potential to mitigate SI and enhance its anti-suicidal effects in TRD patents with SI.

In 2019, a nasal spray containing esketamine, the (*S*)-enantiomer of ketamine, was approved for the TRD, and MDD patients with SI in the United State (U.S.) and Europe. However, a recent study leveraging data from the U.S. Food and Drug Adverse Event Reporting System (FAERS) has highlighted potential adverse reactions and risks associated with the clinical use of esketamine nasal spray, particularly concerning its long-term efficacy, addiction potential, and suicidal risks [6]. Future research should aim for a more personalized approach, including the use of genetic profiling to predict individual responses to esketamine. Arketamine, another enantiomer of ketamine, emerges as potential antidepressant that may avoid the adverse effects commonly associated with ketamine [3, 4].

In pediatric care, esketamine is utilized for inducing anesthesia, sedation during minor surgical procedures, and pain management. Its rapid onset and relatively short duration of action render it appropriate for short-term procedures. However, emergence delirium is a frequent mental complication observed during recover from anesthesia. A recent prospective observational study has shown that a near-anesthetic single-dose of esketamine (0.46 mg/kg: average dose) for anesthesia induction can lead to an increased incidence of emergence delirium in preschool-aged children following minor surgeries [7]. Consequently, clinicians should exercise caution when using esketamine in preschool children undergoing minor surgical procedures.

Electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) are two non-pharmacological treatments employed in managing psychiatric disorders, especially when conventional methods like medications and psychotherapy prove ineffective. Yet,

✉ Kenji Hashimoto
hashimoto@faculty.chiba-u.jp

[1] Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, 1-8-1 Inohana, Chiba 260-8670, Japan

Published online: 12 April 2024

the mechanisms driving the effectiveness of ECT and rTMS remain largely elusive. In this issue, Stuiver et al. [8] explored the cortical excitation/inhibition (E/I) ratios in MDD patients following ECT therapy. At baseline, no significant differences were observed in whole-brain and regional functional E/I ratios between the patients and healthy controls. At a group level, these ratios remained unchanged throughout the ECT sessions. Interestingly, in patients who responded to ECT, there was a significant increase in the frontal functional E/I ratios within the 12–28 Hz frequency range as the treatment progresses. Such changes were not observed in non-responders or healthy controls. This study indicates that the modulation of frontal functional E/I ratios could play a crucial role in ECT's mechanism of action, suggesting the need for further research with large sample sizes to validate these findings.

Wu and Baeken [9] utilized a searchlight-based interregional covariance connectivity approach with baseline ^{18}FDG-PET scan from two previous studies on high-frequency–rTMS in antidepressant-free TRD patients. They found that irrespective of the lateralization of the subgenual anterior cingulate cortex (sgACC), a weaker baseline metabolic functional connection between the sgACC and the left anterior cerebellar areas significantly predicted a better clinical outcome. This finding, which highlights the link between sgACC metabolic connectivity and the left anterior cerebellum without considering sgACC lateralization, suggests the involvement of the left anterior cerebellum in higher-order cognitive processes as part of its predictive value for clinical outcomes.

In this issue, Boylu et al. [10] investigated the effects of rTMS treatment on neuroactive steroids, neurotrophins, and immunological biomarkers in MDD patients. The study found statistically significant increases in brain-derived neurotrophic factor (BDNF) and allopregnanolone, along with decreases in tumor necrosis factor-α, interleukin-1β, dehydroepiandrosterone (DHEA), and DHEA-sulfate levels after rTMS monotherapy. Notably, positive correlations were observed between BDNF levels and the improvement of cognitive functions at one and two months post-treatment. These findings suggests that the therapeutic effects of rTMS may be mediated through neuroendocrine, neurotrophin, and immunological mechanisms.

In conclusion, the articles in this issue offer valuable insights into the therapeutic potential of ketamine and its enantiomers, as well as the mechanisms underlying ECT and rTMS.

Author contributions KH: conceptualization, writing.

Declarations

Conflict of interest Dr. Hashimoto is the inventor of filed patent applications on "The use of *R*-ketamine in the treatment of psychiatric diseases", "(*S*)-norketamine and salt thereof as pharmaceutical", "*R*-ketamine and derivative thereof as prophylactic or therapeutic agent for neurodegeneration disease or recognition function disorder", "Preventive or therapeutic agent and pharmaceutical composition for inflammatory diseases or bone diseases", "*R*-ketamine and its derivatives as a preventive or therapeutic agent for a neurodevelopmental disorder", and "TGF-β1 in the treatment of depression" by the Chiba University. Dr. Hashimoto has also received speakers' honoraria, consultant fee, or research support from Abbott, Daiichi-Sankyo, Meiji Seika Pharma, Seikagaku Corporation, Sumitomo, Taisho, Otsuka, Murakami Farm and Perception Neuroscience. Dr. Hashimoto is Editor at European Archives of Psychiatry and Clinical Neuroscience.

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