

The combined use of rTMS and ketamine in treatment-resistant depression: A case report

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INTRODUCTION

Major depressive disorder (MDD) is a leading cause of disability worldwide, affecting more than 280 million individuals (World Health Organization, 2023). Despite advances in psychopharmacology, treatment-resistant depression (TRD) remains a significant clinical challenge, affecting 30% to 60% of patients with MDD (Mihaljević et al., 2020). TRD is defined as an inadequate response to at least two different classes of antidepressants administered at adequate doses and durations. Patients with TRD often experience persistent depressive symptoms, cognitive dysfunction, functional impairment, and an increased risk of suicidality (Jakuszkowiak-Wojten et al., 2019).

Repetitive transcranial magnetic stimulation (rTMS) and ketamine are two emerging treatments that demonstrate potential effectiveness. Collectively, the combination of these therapies may provide additive benefits in managing TRD, as suggested by existing literature. rTMS is a non-invasive neurostimulation technique that modulates cortical excitability by stimulating the left dorsolateral prefrontal cortex (DLPFC), an area implicated in depression (Filipčić et al., 2018). It enhances neuroplasticity and functional connectivity within mood-regulating circuits (Kumar Mudgal et al., 2022). Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has demonstrated rapid and robust antidepressant effects through enhanced glutamatergic transmission, synaptogenesis, and increased brain-derived neurotrophic factor (BDNF) release (Mihaljević et al., 2020).

Recent studies suggest combining rTMS and ketamine may produce synergistic effects, improving treatment response and durability (Jakuszkowiak-Wojten et al., 2019; Mikellides et al., 2022; Mikellides et al., 2024). However, clinical cases evaluating this combination in real-world settings remain limited.

This report presents a case of severe TRD with psychotic features successfully treated with combined rTMS and intramuscular ketamine, resulting in substantial symptom remission and functional recovery.

CASE PRESENTATION

The patient described in this report provided written informed consent to participate in this study. A 55-year-old Caucasian female presented with persistent severe episodes of MDD with psychotic symptoms according to DSM-5 criteria. She had a five-year history of severe MDD that was resistant to treatment. Previous interventions included consultations with psychologists and psychiatrists, alongside multiple antidepressant regimens trialled over 6 to 9 months with minimal improvement. Initially, a diagnosis of schizoaffective disorder was considered; however, following an extensive clinical assessment conducted in December 2022, this was revised to severe depression with psychotic symptoms.

On examination, the patient reported low mood, fatigue, anhedonia, insomnia with distressing dreams, suicidal ideation, and psychotic features, including visual hallucinations. Her symptoms had escalated over the preceding three years despite trials of various antidepressants, antipsychotics, mood stabilizers, benzodiazepines, and adjunctive medications. The patient's detailed medication regime is summarised in Table 1 below.

Table 1:

Medication	Dose
Mirtazapine	30 mg daily
Venlafaxine	150 mg daily
Clomipramine	150 mg daily
Vortioxetine	20 mg daily
Olanzapine	10 mg daily
Lithium carbonate	1000 mg daily
Haloperidol	10 mg daily
Escitalopram	20 mg daily

Given the severity and unresponsiveness of her symptoms, a combined treatment protocol involving rTMS and intramuscular ketamine was initiated alongside ongoing antidepressant therapy. rTMS was administered using an

FDA-approved triple 3-minute theta-burst stimulation protocol twice weekly during the acute phase, totalling 30 sessions, followed by an additional 12 maintenance sessions over several months. The treatment was well tolerated, with only mild, transient side effects such as occasional mild headaches and brief shooting pain at the stimulation site, resolving spontaneously.

Intramuscular ketamine injections were administered on the same day as rTMS sessions, starting at 0.5 mg/kg for the first session, increasing to 0.75 mg/kg for the second, and reaching 1 mg/kg for subsequent treatments. The acute phase consisted of 12 sessions, followed by an 18-month maintenance phase with gradually tapered frequency. Ketamine treatment was similarly well tolerated, with mild and short-lived side effects such as dizziness and transient sensory disturbances resolving within two hours.

The combined treatment yielded significant improvements. The patient's subjective mood ratings increased from 3-4/10 at baseline to 7-8/10 post-treatment, accompanied by the complete resolution of hallucinations and distressing dreams. Sleep patterns normalized, with the patient achieving 8-9 hours of restful sleep per night. Functionally, she resumed engaging in hobbies such as swimming, Zumba, and enrolling in a cooking course, though she chose not to return to work due to residual anxiety and cognitive overthinking.

CONCLUSION

This case highlights the efficacy and tolerability of combining rTMS and ketamine in treating a patient with TRD and psychotic features. Despite numerous

unsuccessful pharmacological treatments, the patient experienced significant symptom remission, improved sleep, and enhanced functional recovery following this combination therapy. These outcomes align with existing evidence suggesting ketamine's rapid synaptogenesis and NMDA receptor antagonism complement rTMS-induced cortical modulation and neuroplasticity (Mikellides et al., 2022; Mihaljević et al., 2020; Kumar Mudgal et al., 2022).

While these findings are promising, further research is necessary to refine treatment protocols, evaluate long-term outcomes, and explore individualized treatment strategies. Optimizing rTMS coil selection, ketamine dosing regimens, and maintenance strategies may further improve clinical outcomes (Kaczmarek et al., 2021). This case supports the growing evidence that combining neuromodulatory and pharmacological interventions is a viable option for patients with TRD unresponsive to conventional therapies (Sender et al., 2017).

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethics Approval and Consent to Participate: The study was conducted in accordance with ethical standards. Written informed consent was obtained from all individual participants included in the study.

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Authors contributions: Ms. Diana Saabneh: patient interview, scribing, writing of the case report. Mr. Ali Azam Ali Zaher: patient interview, scribing, writing of the case report. Dr. Georgios Mikellides: primary Supervisor

References

- Elboga, G., Demir, B., Gonultas, U., Sahin, S. K., Surme, I., Altindag, A., & Taysi, S. (2023). The effect of repetitive transcranial magnetic stimulation and pharmacotherapy on serum protein S100B in treatment-resistant depression. *Psychiatria Danubina*, 35(4), 500–507.
- Filipčić, I., Šimunović Filipčić, I., Gajšak, T., Milovac, Ž., Sučić, S., Ivezic, E., Zečević Penić, S., Orgulan, I., Šebo, D., Jeleč, V., & Bajić, Ž. (2018). Efficacy and safety of repetitive transcranial magnetic stimulation using an H1-coil or figure-8-coil in the treatment of unipolar major depressive disorder: A study protocol for a randomized controlled trial. *Psychiatria Danubina*, 30(1), 41–46.
- Jakuszkowiak-Wojten, K., Gałuszko-Węgielnik, M., Wilkowska, A., Słupski, J., Włodarczyk, A., Górska, N., Szarmach, J., Szałach, Ł. P., Wiglusz, M. S., Krysta, K., & Cubała, W. J. (2019). Suicidality in treatment-resistant depression: Perspective for ketamine use. *Psychiatria Danubina*, 31(Suppl 3), 258–260.
- Kaczmarek, B., Kowalski, K., Bogudzinska, B., & Piotrowski, P. (2021). Ketamine is a novel drug for depression treatment. *Psychiatria Danubina*, 33(4), 468–474.
- Kumar Mudgal, S., Nath, S., Chaturvedi, J., Kumar Sharma, S., & Joshi, J. (2022). Neuroplasticity in depression: A narrative review with evidence-based insights. *Psychiatria Danubina*, 34(3), 390–397.

- Mikellides, G., Michael, P., Kyriazis, M., & Su, K. P. (2024). Catharsis by ketamine treatment. *Psychiatria Danubina*, 36(1), 146. <https://pubmed.ncbi.nlm.nih.gov/39546530>
- Mikellides, G., Michael, P., Psalta, L., Schuhmann, T., & Sack, A. T. (2022). A retrospective naturalistic study comparing the efficacy of ketamine and repetitive transcranial magnetic stimulation for treatment-resistant depression. *Frontiers in Psychiatry*, 12, 784830. <https://doi.org/10.3389/fpsyt.2021.784830>
- Mihaljević, S., Pavlović, M., Reiner, K., & Čačić, M. (2020). Therapeutic mechanisms of ketamine. *Psychiatria Danubina*, 32(3–4), 325–333.
- Szałach, Ł. P., Lisowska, K. A., Słupski, J., Włodarczyk, A., Górska, N., Szarmach, J., Jakuszkowiak-Wojten, K., Gałuszko-Węgielnik, M., Wiglusz, M. S., Wilkowska, A., & Cubała, W. J. (2019). The immunomodulatory effect of ketamine in depression. *Psychiatria Danubina*, 31(Suppl 3), 252–257.
- Sender, D., Palazzo Nazar, B., Baczynski, T., Paes, F., Fettes, P., Downar, J., Campos, C., Egidio Nardi, A., & Machado, S. (2017). Bilateral DMPFC-rTMS leads to sustained remission in geriatric treatment-resistant depression: A case report. *Psychiatria Danubina*, 29(2), 218–220.
- Włodarczyk, A., Cubała, W. J., Szarmach, J., Małyszko, A., & Wiglusz, M. S. (2019). Shortterm ketamine administration in treatment-resistant depression patients: Focus on adverse effects on the central nervous system. *Psychiatria Danubina*, 31(Suppl 3), 530–533.

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