



## Correspondence

## Intravenous ketamine for treatment-resistant depression patients who have failed to respond to transcranial magnetic stimulation: A case series



## ARTICLE INFO

## Keywords

Depressive disorders  
Ketamine  
TMS  
TRD  
rTMS

## ABSTRACT

**Background:** For individuals with treatment-resistant depression (TRD), transcranial magnetic stimulation (TMS) has become a well-established approach. In the past decade, intravenous (IV) racemic ketamine has also emerged as a potential treatment for TRD. Currently, little data is available on the clinical effects of IV racemic ketamine in TRD patients who experienced TMS-failure.

**Methods:** Twenty-one (21) TRD patients who had failed to respond to a standard course of high-frequency left-dorsolateral prefrontal cortex TMS were subsequently scheduled to receive IV racemic ketamine infusions. The IV racemic ketamine protocol consisted of 0,5 mg/kg infusions over 60 min, 3 times a week over 2 weeks.

**Results:** Treatment was safe with minimal side-effects. Mean baseline MADRS score was  $27.6 \pm 6.4$  (moderate depression), decreasing down to  $18.6 \pm 8.9$  (mild depression) post-treatment. Mean percent improvement was  $34.5 \% \pm 21.1$  from baseline to post-treatment. Paired sample *t*-test showed significant MADRS score decrease pre- to post-treatment [ $t(20) = 7.212, p < .001$ ]. Overall, four (4) patients (19.0 %) responded and two (2) of those achieved remission (9.5 %).

**Limitations:** Limitations of this case series include its retrospective and uncontrolled open-label nature, the lack of self-rating and standardized adverse events questionnaires, as well as follow-ups beyond the immediate treatment period.

**Conclusions:** Novel ways to increase the clinical effects of ketamine are being explored. We discuss potential combination approaches of ketamine with other modalities to augment its effects. Given the global burden of TRD, novel approaches are needed to curb the current mental health epidemic around the world.

### 1. Introduction

Between 30 and 40 % of patients suffering from major depressive disorder will develop treatment-resistant depression (TRD), classically described as a lack of satisfactory response to two or more adequate antidepressant trials (McAllister-Williams et al., 2020). For these patients, a well-established approach is transcranial magnetic stimulation (TMS) (Milev et al., 2016). Current hypotheses suggest that TMS can increase neuroplasticity through complex neurobiochemical mechanisms, such as agonistic effect on NMDA receptors and modulation of dopaminergic and gamma-aminobutyric acid activity (Miron et al., 2021). It is also theorized that standard high-frequency (HF) left dorsolateral prefrontal cortex (L-DLPFC) TMS can help normalize aberrant large-scale brain network activity through the salience network, decreasing hyperactivity in the default-mode network and reinforcing executive network activity (Miron et al., 2021). Unfortunately, not all patients with TRD will respond to TMS.

Racemic intravenous (IV) ketamine is an emerging approach for TRD. Current theories suggest that ketamine can influence neuroplasticity through antagonism of NMDA receptors, initiating complex cellular and molecular cascade resulting in antidepressant effects (Swainson et al., 2021). At the network level, ketamine could also quash the negative attractor state in the lateral orbitofrontal cortex and ventrolateral prefrontal cortex, decreasing ruminations (Rolls, 2016). Given the limited therapeutic options remaining for TMS-resistant TRD

patients, there is an interest in assessing the effectiveness of ketamine in that population.

### 2. Methods

Between September 2018 and October 2022, twenty-one (21) TRD patients who received and failed to respond to a standard course of HF L-DLPFC TMS were included. TMS was delivered either on a MagVenture system (B70 coil) using the BeamF3 algorithm (20 Hz, 3000 pulses, 30 trains, 5 s ON, 25 s OFF, 120 % motor threshold [MT] intensity, 15 min) or a Brainsway system (H1 coil) (18 Hz, 1980 pulses, 55 trains, 2 s ON, 20 s OFF, 120 % MT, ~20 min). Patients were subsequently scheduled to receive IV racemic ketamine, which consisted of 0,5 mg/kg infusions over 60 min, three (3) times a week over two (2) weeks (Swainson et al., 2021).

Patients were queried daily about any side effects on treatment days. Effectiveness outcomes were assessed using the Montgomery-Åsberg Depression Scale (MADRS) pre- and post-treatment. Baseline MADRS was completed immediately before the first session, and post-treatment MADRS was completed immediately after the last session. Outcomes of interest included mean percent improvement, remission rates (<10 score post-treatment), and response rates (score reductions of  $\geq 50$  % from baseline score). We included remitters in responders.

<https://doi.org/10.1016/j.jad.2023.04.019>

Received 8 November 2022; Received in revised form 18 March 2023; Accepted 14 April 2023

Available online 17 April 2023

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### 3. Results

Mean age was 49.8 ( $\pm 12.5$ ) years and 33.3 % of patients were women. More than half (57.1 %) suffered from comorbid anxiety and three (3) had bipolar TRD. No serious adverse events occurred. 12/21 (57.1 %) of patients reported mild to moderate dissociation during the infusion, one patient reported temporary nausea during the infusion, one patient reported increased insomnia during the treatment course, and two patients reported increased anxiety during one of the infusions. Mean baseline MADRS score was  $27.6 \pm 6.4$  (moderate depression), decreasing to  $18.6 \pm 8.9$  (mild depression) post-treatment (see Fig. 1). Mean percent improvement post-treatment was  $34.5 \% \pm 21.1$ . Paired sample *t*-test showed significant MADRS score decrease pre- to post-treatment [ $t(20) = 7.212, p < .001$ ]. Overall, four (4) patients (19.0 %) responded, and two (2) of those achieved remission (9.5 %).

### 4. Discussion

The treatment was safe with minimal side effects. Response and remission rates to IV ketamine in our cohort were 19.0 % and 9.5 %, comparable to what was reported in a retrospective cohort comparing outcomes of IV ketamine in TRD patients with or without a history of neuromodulation (20.0 % response and 10.9 % remission in the group with a history of neuromodulation) (Rodrigues et al., 2020). In non-TMS resistant TRD populations, response and remission rates following six ketamine infusions have been reported to be around 51 % and 26 %, respectively (Swainson et al., 2021). The fact that our cohort had a higher degree of treatment resistance (TMS failure) could explain the limited clinical effects observed.

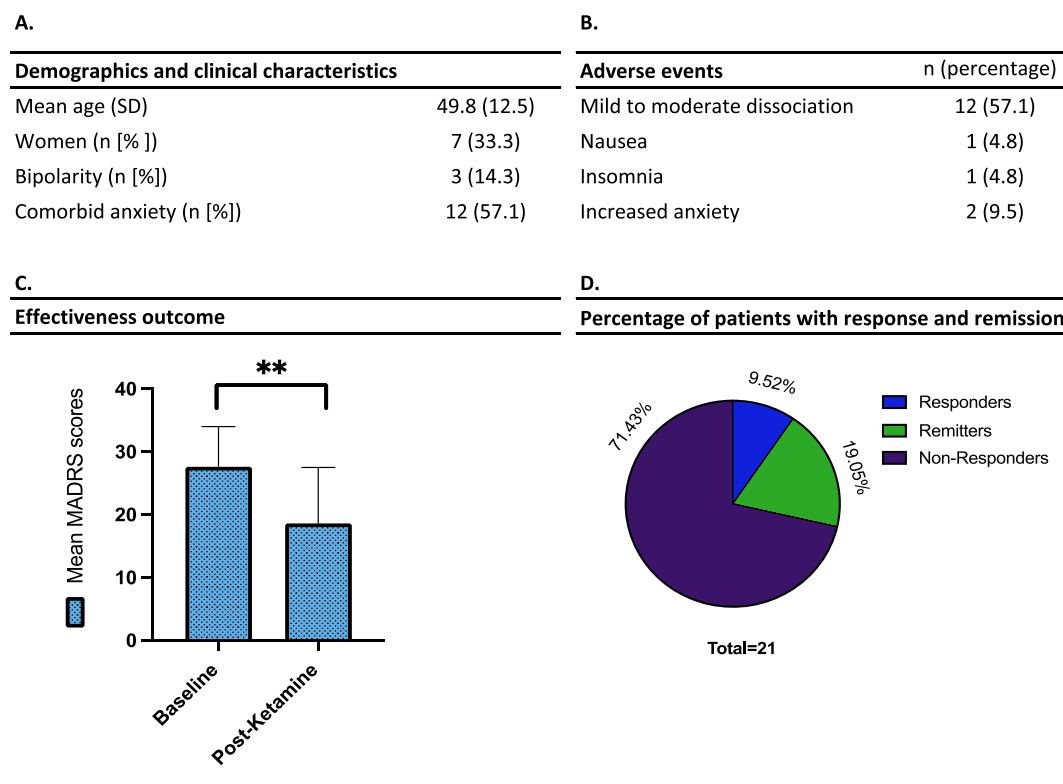
Novel ways to increase the clinical effects of ketamine need to be explored. A promising approach is the combination of ketamine and talk therapy: ketamine-assisted psychotherapy (KAP). While no single definition of KAP exists, the most integrative approach offers preparatory

psychotherapy sessions before the intervention, followed by integrative sessions during and after the treatment period (Dore et al., 2019; Joneborg et al., 2022). The addition of psychotherapy could stabilize the positive neuroplastic effects of ketamine, while the short-term increase in neuroplasticity induced by ketamine could facilitate the integration of new skills and coping mechanisms (Dore et al., 2019; Joneborg et al., 2022). The dissociative effect of ketamine is also thought to be therapeutic in nature, helping patients reevaluate long-held dysfunctional schemata, a phenomenon that could be harnessed by concurrent integrative psychotherapy (Dore et al., 2019; Joneborg et al., 2022). Also, a recent study combining ketamine with automated self-association training was shown to be superior to ketamine alone for depression (Price et al., 2022). Lastly, our group recently published a case report on a patient suffering from bipolar depression who had limited response to TMS and ketamine individually, but who experienced lasting remission following combination treatment with both modalities (Elkrief et al., 2022).

Limitations include the retrospective and uncontrolled open-label nature of this case series. MADRS was the only measure of depression severity and there were no self-rated questionnaires, which could better reflect patient's perspectives on their improvement (McAllister-Williams et al., 2020). Additionally, no standardized adverse event or dissociation questionnaires were used. Also, we did not collect MADRS scores at follow-up beyond the immediate treatment period. More data on this aspect would have been helpful, given the issue raised about the durability of effects following acute ketamine treatment (Sanacora et al., 2017). Still, there is now evidence that maintenance treatment is feasible, safe, and effective (Alnefeesi et al., 2022).

### 5. Conclusion

In summary, this case series supports the notion that racemic IV ketamine is safe and well-tolerated for TRD. Even though clinical effects



**Fig. 1.** A. Demographics. B. Adverse events. C. Montgomery-Åsberg Depression Rating Scale (MADRS). D. Percentage of response (i.e.,  $<50$  % reduction in MADRS score) and remission (i.e.,  $<10$  score post-treatment) rates.

were limited, improvement is still possible even in highly treatment-refractory patients. Other approaches to explore include combination with psychotherapeutic techniques and TMS. Given the global burden of TRD, novel approaches are needed to curb the current mental health epidemic around the world.

### CRedit authorship contribution statement

OP wrote the first draft of the manuscript. OP and VDJ were responsible for statistical analyses. PL, VDJ, CLP, LE, MR and NG revised the manuscript. JPM designed and supervised the study and led major revisions to the first draft of the manuscript to create the final version. All authors approved the final version of the manuscript.

### Conflict of interest

All authors declare that they have no conflicts of interest related to this work.

### Acknowledgments

We would like to thank our dedicated nursing staff Sylvie Tieu, Ana Baker, and Georgina Yavo, for their role in data collection and patient care.

### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### References

- Alnefeesi, Y., Chen-Li, D., Krane, E., Jawad, M.Y., Rodrigues, N.B., Ceban, F., Vincenzo, J.D.D., Meshkat, S., Ho, R.C.M., Gill, H., Teopiz, K.M., Cao, B., Lee, Y., McIntyre, R.S., Rosenblat, J.D., 2022. Real-world effectiveness of ketamine in treatment-resistant depression: a systematic review & meta-analysis. *J. Psychiatr. Res.* 151, 693–709. <https://doi.org/10.1016/j.jpsychires.2022.04.037>.
- Dore, J., Turnipseed, B., Dwyer, S., Turnipseed, A., Andries, J., Ascani, G., Monnette, C., Huidekoper, A., Strauss, N., Wolfson, P., 2019. Ketamine assisted psychotherapy (KAP): patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *J. Psychoactive Drugs* 51, 189–198. <https://doi.org/10.1080/02791072.2019.1587556>.
- Elkrief, L., Payette, O., Foucault, J.-N., Longpré-Poirier, C., Richard, M., Jodoin, V.D., Lespérance, P., Miron, J.-P., 2022. Transcranial magnetic stimulation and intravenous ketamine combination therapy for treatment-resistant bipolar depression: a case report. *Frontiers Psychiatry* 13, 986378. <https://doi.org/10.3389/fpsy.2022.986378>.
- Joneborg, I., Lee, Y., Vincenzo, J.D.D., Ceban, F., Meshkat, S., Lui, L.M.W., Fancy, F., Rosenblat, J.D., McIntyre, R.S., 2022. Active mechanisms of ketamine-assisted psychotherapy: a systematic review. *J. Affect. Disord.* 315, 105–112. <https://doi.org/10.1016/j.jad.2022.07.030>.
- McAllister-Williams, R.H., Arango, C., Blier, P., Demyttenaere, K., Falkai, P., Gorwood, P., Hopwood, M., Javed, A., Kasper, S., Malhi, G.S., Soares, J.C., Vieta, E.,

- Young, A.H., Papadopoulos, A., Rush, A.J., 2020. The identification, assessment and management of difficult-to-treat depression: an international consensus statement. *J. Affect. Disord.* 267, 264–282. <https://doi.org/10.1016/j.jad.2020.02.023>.
- Milev, R.V., Giacobbe, P., Kennedy, S.H., Blumberger, D.M., Daskalakis, Z.J., Downar, J., Modirrousta, M., Patry, S., Vila-Rodriguez, F., Lam, R.W., MacQueen, G.M., Parikh, S.V., Ravindran, A.V., Group, C.D.W., 2016. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder. *Can. J. Psychiatry* 61, 561–575. <https://doi.org/10.1177/0706743716660033>.
- Miron, J.-P., Jodoin, V.D., Lespérance, P., Blumberger, D.M., 2021. Repetitive transcranial magnetic stimulation for major depressive disorder: basic principles and future directions. *Ther. Adv. Psychopharmacol.* 11, 204512532110426. <https://doi.org/10.1177/20451253211042696>.
- Price, R.B., Spotts, C., Panny, B., Griffio, A., Degutis, M., Cruz, N., Bell, E., Do-Nguyen, K., Wallace, M.L., Mathew, S.J., Howland, R.H., 2022. A novel, brief, fully automated intervention to extend the antidepressant effect of a single ketamine infusion: a randomized clinical trial. *Am. J. Psychiatr.* <https://doi.org/10.1176/appi.ajp.20220216>.
- Rodrigues, N.B., Siegel, A., Lipsitz, O., Cha, D.S., Gill, H., Nasri, F., Simonson, K., Shekotiikhina, M., Lee, Y., Subramaniapillai, M., Kratiuk, K., Lin, K., Ho, R., Mansur, R.B., McIntyre, R.S., Rosenblat, J.D., 2020. Effectiveness of intravenous ketamine in mood disorder patients with a history of neurostimulation. *CNS Spectr.* 1–7. <https://doi.org/10.1017/s1092852920002187>.
- Rolls, E.T., 2016. A non-reward attractor theory of depression. *Neurosci. Biobehav. Rev.* 68, 47–58. <https://doi.org/10.1016/j.neubiorev.2016.05.007>.
- Sanacora, G., Frye, M.A., McDonald, W., Mathew, S.J., Turner, M.S., Schatzberg, A.F., Summergrad, P., Nemeroff, C.B., 2017. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry* 74. <https://doi.org/10.1001/jamapsychiatry.2017.0080>, 399–7.
- Swainson, J., McGirr, A., Blier, P., Brietzke, E., Richard-Devantoy, S., Ravindran, N., Blier, J., Beaulieu, S., Frey, B.N., Kennedy, S.H., McIntyre, R.S., Milev, R.V., Parikh, S.V., Schaffer, A., Taylor, V.H., Tourjman, V., Ameringen, M., van, Yatham, L.N., Ravindran, A.V., Lam, R.W., 2021. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the use of racemic ketamine in adults with major depressive disorder: recommendations Du Groupe De Travail Du Réseau Canadien Pour Les Traitements De L'humeur Et De L'anxiété (Canmat) Concernant L'utilisation De La Kétamine Racémique Chez Les Adultes Souffrant De Trouble Dépressif Majeur. *Can. J. Psychiatry* 66, 113–125. <https://doi.org/10.1177/0706743720970860>.

Olivier Payette<sup>a</sup>, Paul Lespérance<sup>a,b</sup>, Véronique Desbeaumes Jodoin<sup>a</sup>, Christophe Longpré-Poirier<sup>b</sup>, Laurent Elkrief<sup>b</sup>, Maxime Richard<sup>b</sup>, Nicolas Garel<sup>c</sup>, Jean-Philippe Miron<sup>a,b,\*</sup>

<sup>a</sup> Centre Hospitalier de l'Université de Montréal (CHUM) et Centre de Recherche du CHUM (CRCHUM), Université de Montréal, QC, Canada

<sup>b</sup> Département de Psychiatrie et d'Addictologie, Faculté de Médecine, Université de Montréal, QC, Canada

<sup>c</sup> Department of Psychiatry, Faculty of Medicine, McGill University, Ludmer Research & Training Building, 1033 Av. des Pins, Montréal, Quebec H3A 1A1, Canada

\* Corresponding author at: Centre Hospitalier de l'Université de Montréal (CHUM) et Centre de Recherche du CHUM (CRCHUM), Université de Montréal, QC, Canada.

E-mail address: [jean-philippe.miron.1@umontreal.ca](mailto:jean-philippe.miron.1@umontreal.ca) (J.-P. Miron).