

Esketamine-Associated Lower Urinary Tract Symptoms Suggestive of Bladder Overactivity in Treatment-Resistant Depression: A Case Report

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Case Report

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Abstract

Background

Intranasal esketamine is an approved therapy for treatment-resistant depression and is recognized for its rapid and effective antidepressant effects. Although ketamine-associated cystitis has been documented in recreational users, the urinary safety profile of therapeutic esketamine remains incompletely characterized. Functional lower urinary tract disturbances suggestive of bladder overactivity have not yet been reported in the scientific literature among patients receiving esketamine for treatment-resistant depression.

Case presentation:

We present the case of a middle-aged male patient with severe treatment-resistant depression who developed urinary urgency and pelvic discomfort shortly after initiating intranasal esketamine. Urological evaluation showed no evidence of infection or inflammation, and the urine culture was negative. Partial symptomatic control was achieved with mirabegron. Urinary symptoms resolved after spacing the frequency of esketamine administration.

Conclusions

This case suggests a probable association between intranasal esketamine and lower urinary tract symptoms suggestive of bladder overactivity in the absence of inflammatory findings, with symptoms resolving after spacing of treatment administration.

Background

Intranasal esketamine has emerged as an effective therapeutic option for major depressive disorder, particularly in patients with treatment-resistant depression (TRD) (1–4). Acting primarily as a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, esketamine modulates glutamatergic neurotransmission and promotes rapid synaptic plasticity, distinguishing it from conventional monoaminergic antidepressants (5,6). Randomized controlled trials have consistently demonstrated its efficacy when used in combination with an oral antidepressant, leading to significant reductions in depressive symptoms and higher remission rates compared to placebo (1,5,7). Evidence from real-world studies further corroborates its effectiveness and safety in routine clinical practice (8–10); however, its full adverse event profile remains incompletely characterized particularly with regard to potential effects on the lower urinary tract.

In contrast, ketamine, particularly in its racemic form and with chronic recreational use, has consistently been associated with urological toxicity, most notably ketamine-induced cystitis (KIC) (11). The

underlying pathophysiology remains incompletely understood but is thought to involve direct urothelial toxicity, inflammatory responses, and microvascular injury (11). Importantly, clinical evidence suggests that early recognition and cessation of ketamine use may lead to partial or complete reversal of urinary symptoms, highlighting a dose- and exposure-dependent mechanism of injury (11–13).

We present the case of a middle-aged male patient with treatment-resistant depression who developed lower urinary tract symptoms suggestive of bladder overactivity shortly after initiating intranasal esketamine. To our knowledge, this is the first reported case of non-inflammatory lower urinary tract symptoms consistent with bladder overactivity in a patient receiving intranasal esketamine for TRD.

Case presentation

A 50-year-old married male, father of two, and working as a merchant, presented with a long-standing history of treatment-resistant depression. He reported being under psychiatric treatment for approximately 10 years, though he believed depressive symptoms had been present for a longer period. During this time, he experienced only partial responses to multiple treatments, describing transient improvements of up to 80% without ever achieving full remission.

Over the previous two years, his condition had significantly deteriorated, with pervasive low mood, hopelessness, anhedonia, and marked functional impairment. He reported spending more than 12 hours per day lying down after work, with reduced occupational performance leading to financial difficulties and accumulated debt. Sleep was fragmented, with frequent nocturnal awakenings. He described a chronic passive death wish, stating that his “internal dialogue is disturbing,” although he denied active suicidal intent due to his responsibility towards his daughters.

Additional symptoms included reduced appetite, irritability, impulsivity, persistent anxiety, psychomotor restlessness, and significant cognitive impairment, characterized by poor concentration, mental fog, and distractibility. He rated his subjective suffering as 10 out of 10 and reported emotional blunting, including an inability to cry despite feeling distressed. His medical history was notable for prior bariatric surgery 15 years earlier, with subsequent discontinuation of vitamin supplementation. He was also an active smoker and reported alcohol misuse.

At the time of evaluation, the patient was changing his medication and receiving vortioxetine 10 mg, lamotrigine 200 mg, lurasidone 40 mg, and quetiapine 100 mg, with prior adequate trials of escitalopram, fluoxetine, sertraline, bupropion, and valproate without satisfactory response. Given the severity and refractoriness of symptoms, intranasal esketamine was initiated at a dose of 84 mg (three 28 mg devices). During treatment, the oral pharmacological regimen was gradually adjusted, ultimately consisting of desvenlafaxine 100 mg, quetiapine 100 mg, lisdexamfetamine 30 mg, and brexpiprazole 1 mg. The baseline Hamilton Depression Rating Scale (HAM-D) (14,15) score was 33, indicating severe depression.

Following the second administration of esketamine, the patient developed intense urinary urgency, without dysuria or fever. Oxybutynin 5 mg was prescribed by a non-specialist physician prior to a urological evaluation, with no clinical improvement. Urological evaluation raised suspicion of cystitis; however, urinalysis revealed no pyuria, hematuria, or signs of infection, and urine culture was negative (Supplemental 1). Blood tests, including renal function, were within normal limits, and urinary tract ultrasound showed no abnormalities. Vitamin B12 levels were 376 pg/mL and were subsequently supplemented. Mirabegron 50 mg was then initiated, resulting in partial symptomatic control. Urinary symptoms persisted throughout the induction phase and resolved only after spacing of esketamine administration to weekly sessions. Mirabegron was maintained for 45 days and then discontinued without recurrence of urinary complaints. Esketamine treatment was continued on a weekly basis for one year, with no further urinary symptoms. To further assess causality, the adverse event was evaluated using the Naranjo Adverse Drug Reaction Probability Scale, yielding a score of 6, consistent with a probable adverse drug reaction (Supplemental 2)

In parallel, depressive symptoms improved rapidly, with a clinically significant response observed within the first month of treatment and sustained over 12 months. Full symptomatic remission was achieved after 9 months of treatment (Fig 1).

Discussion

This case describes a patient with TRD who developed acute lower urinary tract symptoms shortly after initiation of intranasal esketamine, in the absence of laboratory or imaging evidence of infection or inflammatory cystitis. The temporal relationship, persistence during the induction phase, and resolution after treatment spacing support a probable pharmacological association, suggesting a non-inflammatory, likely functional mechanism. Although no urodynamic evaluation was performed, the symptom profile was clinically suggestive of a functional bladder disturbance.

Lower urinary tract symptoms are well described among individuals with chronic recreational use of racemic ketamine, reflecting a spectrum of urological toxicity related to cumulative exposure (11,16,17). Within this spectrum, ketamine-induced cystitis (KIC) represents the most severe and well-characterised phenotype, typically associated with sustained high-dose exposure and inflammatory bladder involvement that may extend to the upper urinary tract (16,18). Proposed mechanisms include urothelial toxicity, inflammatory injury, and microvascular damage (17,19). Alternative explanations should also be considered. The patient had several potential confounding factors, including tobacco use, alcohol misuse, nutritional issues following bariatric surgery, concomitant psychotropic adjustments, and significant baseline anxiety symptoms. Stimulant exposure via lisdexamfetamine could theoretically contribute to autonomic symptoms. However, these factors did not show a temporal association comparable to that observed with esketamine initiation and symptom evolution.

Conversely, a previously reported case described a 28-year-old female with TRD who received sublingual followed by oral ketamine and experienced improvement in depressive symptoms, as reported by both

the patient and the treating team. Treatment, however, was complicated by the development of KIC, leading to discontinuation due to concerns about potential irreversible bladder and upper urinary tract injury. Urinary symptoms resolved completely within three weeks after cessation of ketamine, but this was accompanied by worsening of depressive symptoms (13).

Although direct head-to-head comparisons between ketamine and intranasal esketamine are limited, available evidence suggests broadly similar efficacy, with a more consistently characterised safety profile for esketamine in clinical trials (5,20–22). While urological toxicity is well established in the context of chronic racemic ketamine exposure, particularly in recreational settings, such findings have not been consistently reported with therapeutic intranasal esketamine (4,5,16,23). Observational data indicate that up to 26.6% of recent ketamine users report urinary symptoms, reinforcing the association between cumulative exposure and lower urinary tract dysfunction (18). In contrast, in clinical trials of intranasal esketamine, urinary adverse events have been infrequently reported, typically occurring in fewer than 5% of patients and generally limited to mild, nonspecific symptoms, without evidence of inflammatory bladder toxicity (4,5,21).

The mechanism underlying this presentation remains uncertain but may reflect a functional effect of esketamine on bladder control rather than structural or inflammatory injury (11,24,25). As a non-competitive NMDA receptor antagonist, esketamine modulates glutamatergic neurotransmission involved in central autonomic regulation of lower urinary tract function (11,25,26). Transient alterations in neural circuits regulating detrusor activity may therefore explain symptoms such as urgency in the absence of detectable inflammation (26). Neural regulation of micturition involves a complex network integrating the prefrontal cortex, periaqueductal gray matter, pontine micturition center, and spinal pathways. Given the role of glutamatergic neurotransmission in these circuits, transient NMDA receptor modulation by esketamine could hypothetically alter sensory processing or detrusor control, leading to urgency symptoms in susceptible individuals. The temporal pattern observed here further supports a reversible, exposure-dependent effect, distinct from the cumulative toxicity described in KIC. Interestingly, symptoms emerged specifically during the induction phase, characterized by more frequent administrations and greater short-term exposure intensity. This observation raises the possibility that peak cumulative exposure during induction, rather than long-term cumulative dose alone, may transiently influence neural circuits regulating micturition.

This case highlights a potentially underrecognized pattern of urinary adverse effects associated with intranasal esketamine, in which symptoms may emerge during the induction phase and resolve with dose-frequency adjustment. Recognition of this presentation is clinically relevant, as it may help avoid unnecessary investigations and support continuation of an otherwise effective treatment for TRD.

Patient perspective: “From the very first administrations of intranasal esketamine, my distress decreased significantly. This led to a substantial reduction in thoughts of death. I am now able to drive without looking at an oncoming truck and thinking about crashing my car into it. I feel more organized again and have been able to return to my previous level of work performance, including selling as I used

to. Overall, I feel that I am recovering well. I often tell my family that it feels as though I have been “acquitted,” but I am still wearing an ankle monitor—I remain constantly vigilant, watching for any signs that symptoms might return and considering what more I can do to continue improving.”

This report has important limitations. Objective assessment tools such as bladder diaries, symptom scales, or urodynamic studies were not performed. Therefore, the diagnosis of bladder overactivity remains clinically inferred. Furthermore, causal interpretation is limited by the observational nature of a single case report.

Conclusion

This case suggests that non-inflammatory lower urinary tract symptoms may occur during intranasal esketamine treatment, and may resolve with dose-frequency adjustment. Awareness of this pattern may help prevent unnecessary discontinuation of an effective therapeutic strategy for TRD. These observations also support the systematic monitoring of lower urinary tract symptoms in real-world esketamine cohorts, particularly during the induction phase, in order to determine incidence, predictors, and clinical significance.

Declarations

This case report was prepared and reported in accordance with the CARE guidelines and was approved by the Research Ethics Committee of the Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Brazil (CAAE: 98022826.1.0000.5336; approval number: 8.458.836). Written informed consent was obtained from the patient for the use and publication of his clinical information. Clinical trial number: not applicable.

Consent for publication:

Written informed consent was obtained from the patient for publication of this case report and the accompanying clinical data.

Availability of data and materials:

All data relevant to this case report are included in the article and its supplementary information files. Additional clinical data are not publicly available to protect patient confidentiality.

Abbreviations:

HAM-D: Hamilton Depression Rating Scale, KIC: Ketamine-induced cystitis, LUTS: Lower urinary tract symptoms, NMDA: N-methyl-D-aspartate, TRD: Treatment-resistant depression

Competing interests:

C.O.L. has served on speakers' bureaus and/or as a consultant for Johnson & Johnson, Merck, Novo Nordisk, Lundbeck, Eli Lilly, Viartis, Apsen, Libbs, Eurofarma, Brace Pharma, Aché, EMS, FQM, and Daiichi Sankyo during the past three years. She has also received travel support, including airfare and accommodation, from Johnson & Johnson, Merck, Eli Lilly, and Libbs to attend scientific meetings.

L.S. has served as a speaker and consultant for Johnson & Johnson and has received travel support, including airfare and accommodation, from Johnson & Johnson to attend scientific meetings. He has received research funding from Johnson & Johnson and Neumora.

M.F.J. has received consultancy fees, advisory board honoraria, and/or lecture honoraria from Janssen (Johnson & Johnson), Lundbeck, Takeda, LivaNova, Neurocentrx, Abdi Ibrahim, Hikma, Daiichi Sankyo, Novartis, EMS, Brace Pharma, WHO, UNESCO, CNPq, FAPESP, the Dutch Foundation, and other pharmaceutical companies with products used in affective and related disorders. He receives publishing royalties from Cambridge University Press, Springer Nature, and Elsevier. M.F.J. holds a U.S. patent related to oral ketamine for the treatment, control, or prevention of depressive disorders.

K.F. has served as a speaker for Johnson & Johnson and has received support to attend scientific meetings from Lundbeck and Adium.

M.C.M.C. has served as a speaker for Janssen and Apsen and has received support from Janssen to attend scientific meetings.

D.C.P. has served as a speaker for Adium, Lundbeck, Apsen, Libbs, Aché, Biolab, Abbott, Eurofarma, and Torrent.

T.W.V. declares no competing interests.

V.A. declares no competing interests.

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Authors'contributions:

C.O.L., L.S., K.F., D.C.P., and M.C.M.C. contributed to the conception and design of the case report. C.O.L. was responsible for the clinical management and follow-up of the patient, data collection, and review of the medical records. C.O.L. and V.A. performed the literature review. C.O.L. and L.S. drafted the initial version of the manuscript and prepared the figures and tables. M.F.J., T.W.V, D.C.P., K.F., and M.C.M.C. critically reviewed and edited the manuscript. C.O.L. contributed to the interpretation of the clinical findings and proposed mechanisms. L.S., M.F.J., and T.W.V provided scientific supervision. All authors read and approved the final manuscript.

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References

1. Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, et al. Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). *Int J Neuropsychopharmacol* 1º de outubro de. 2019;22(10):616–30. 10.1093/ijnp/pyz039.
2. Fountoulakis KN, Saitis A, Schatzberg AF. Esketamine Treatment for Depression in Adults: A PRISMA Systematic Review and Meta-Analysis. *Am J Psychiatry* 1º de março de. 2025;182(3):259–75. 10.1176/appi.ajp.20240515.
3. Kim J, Lee SH, Shin C, Han KM, Cho SJ, Hong N, et al. A Multi-Center, Open-Label, Single-Arm Study to Investigate the Early Effectiveness of Esketamine Nasal Spray in Patients with Treatment-Resistant Depression Using a Mobile Self-Monitoring Application. *Pharmaceuticals* 30 de agosto de. 2024;17(9):1143. 10.3390/ph17091143.
4. Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. *Am J Psychiatry*. 1º de junho de. 2019;176(6):428–38. 10.1176/appi.ajp.2019.19020172
5. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA Psychiatry* 1º de setembro de. 2019;76(9):893. 10.1001/jamapsychiatry.2019.1189.
6. McIntyre RS, Jain R. Glutamatergic Modulators for Major Depression from Theory to Clinical Use. *CNS Drugs* novembro de. 2024;38(11):869–90. 10.1007/s40263-024-01114-y.
7. Ochs-Ross R, Daly EJ, Zhang Y, Lane R, Lim P, Morrison RL, et al. Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression—

- TRANSFORM-3. *Am J Geriatr Psychiatry* fevereiro de. 2020;28(2):121–41. 10.1016/j.jagp.2019.10.008.
8. De Oliveira Lapa C, Viola T, Delfino R, Dutra L, Rubira G, Rodrigues RJK, et al. Systematic review and meta-analysis of intranasal esketamine for treatment-resistant depression: Evidence from real-world studies. *J Affect Disord* maio de. 2026;401:121257. 10.1016/j.jad.2026.121257.
 9. Martinotti G, Vita A, Fagiolini A, Maina G, Bertolino A, Dell’Osso B, et al. Real-world experience of esketamine use to manage treatment-resistant depression: A multicentric study on safety and effectiveness (REAL-ESK study). *J Affect Disord* dezembro de. 2022;319:646–54. 10.1016/j.jad.2022.09.043.
 10. Molero P, Ibañez A, De Diego-Adeliño J, Ramos-Quiroga JA, García Dorado M, López Rengel PM, et al. A Real-World Study on the Use, Effectiveness, and Safety of Esketamine Nasal Spray in Patients with Treatment-Resistant Depression: INTEGRATE Study. *Adv Ther* maio de. 2025;42(5):2335–53. 10.1007/s12325-025-03149-z.
 11. Anderson J, Zhou D, Cao J, McDonald D, Guenther M, Hasoon M. Ketamine-Induced Cystitis: A Comprehensive Review of the Urologic Effects of This Psychoactive Drug. *Health Psychol Res* 14 de setembro de. 2022;10(3):1. 10.52965/001c.38247.
 12. Yek J, Sundaram P, Aydin H, Kuo T, Ng LG. The clinical presentation and diagnosis of ketamine-associated urinary tract dysfunction in Singapore. *Singap Med J* dezembro de. 2015;56(12):660–4. 10.11622/smedj.2015185. quiz 665.
 13. Chang M, Juruena MF, Young AH. Ketamine cystitis following ketamine therapy for treatment-resistant depression – case report. *BMC Psychiatry* 2 de janeiro de. 2024;24(1):9. 10.1186/s12888-023-05468-3.
 14. Hamilton M, A RATING SCALE FOR, DEPRESSION. *J Neurol Neurosurg Psychiatry*. 1º de fevereiro de. 1960;23(1):56–62. 10.1136/jnnp.23.1.56
 15. Freire MÁ, Figueiredo VLMD, Gomide A, Jansen K, Silva RAD, Magalhães PVDS, et al. Escala Hamilton: estudo das características psicométricas em uma amostra do sul do Brasil. *J Bras Psiquiatr* dezembro de. 2014;63(4):281–9. 10.1590/0047-20850000000036.
 16. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine-Associated Ulcerative Cystitis: A New Clinical Entity. *Urol* maio de. 2007;69(5):810–2. 10.1016/j.urology.2007.01.038.
 17. Chen CL, Wu ST, Cha TL, Sun GH, Meng E. Molecular Pathophysiology and Potential Therapeutic Strategies of Ketamine-Related Cystitis. *Biology*. 24 de março de 2022;11(4):502. 10.3390/biology11040502
 18. Winstock AR, Mitcheson L, Gillatt DA, Cottrell AM. The prevalence and natural history of urinary symptoms among recreational ketamine users. *BJU Int* dezembro de. 2012;110(11):1762–6. 10.1111/j.1464-410X.2012.11028.x.
 19. Baker SC, Shabir S, Georgopoulos NT, Southgate J. Ketamine-Induced Apoptosis in Normal Human Urothelial Cells. *Am J Pathol* maio de. 2016;186(5):1267–77. 10.1016/j.ajpath.2015.12.014.

20. Correia-Melo FS, Leal GC, Vieira F, Jesus-Nunes AP, Mello RP, Magnavita G, et al. Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: A randomized, double-blind, non-inferiority study. *J Affect Disord* março de. 2020;264:527–34. 10.1016/j.jad.2019.11.086.
21. Wajs E, Aluisio L, Holder R, Daly EJ, Lane R, Lim P, et al. Esketamine Nasal Spray Plus Oral Antidepressant in Patients With Treatment-Resistant Depression: Assessment of Long-Term Safety in a Phase 3, Open-Label Study (SUSTAIN-2). *J Clin Psychiatry* 28 de abril de. 2020;81(3). 10.4088/jcp.19m12891.
22. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* fevereiro de. 2000;47(4):351–4. 10.1016/S0006-3223(99)00230-9.
23. Chu PS. 'Street ketamine'--associated bladder dysfunction: a report of ten cases.
24. Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA et al. A Randomized Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression. *ARCH GEN PSYCHIATRY*. 2006;63.
25. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med* março de. 2016;22(3):238–49. 10.1038/nm.4050.
26. De Groat WC, Griffiths D, Yoshimura N. Neural Control of the Lower Urinary Tract. Em: Terjung R, organizador. *Comprehensive Physiology* [Internet]. 1º ed. Wiley; 2014 [citado 21 de abril de 2026]. pp. 327–96. Disponível em: <https://onlinelibrary.wiley.com/doi/10.1002/cphy.c130056> doi:10.1002/cphy.c130056.

Figures

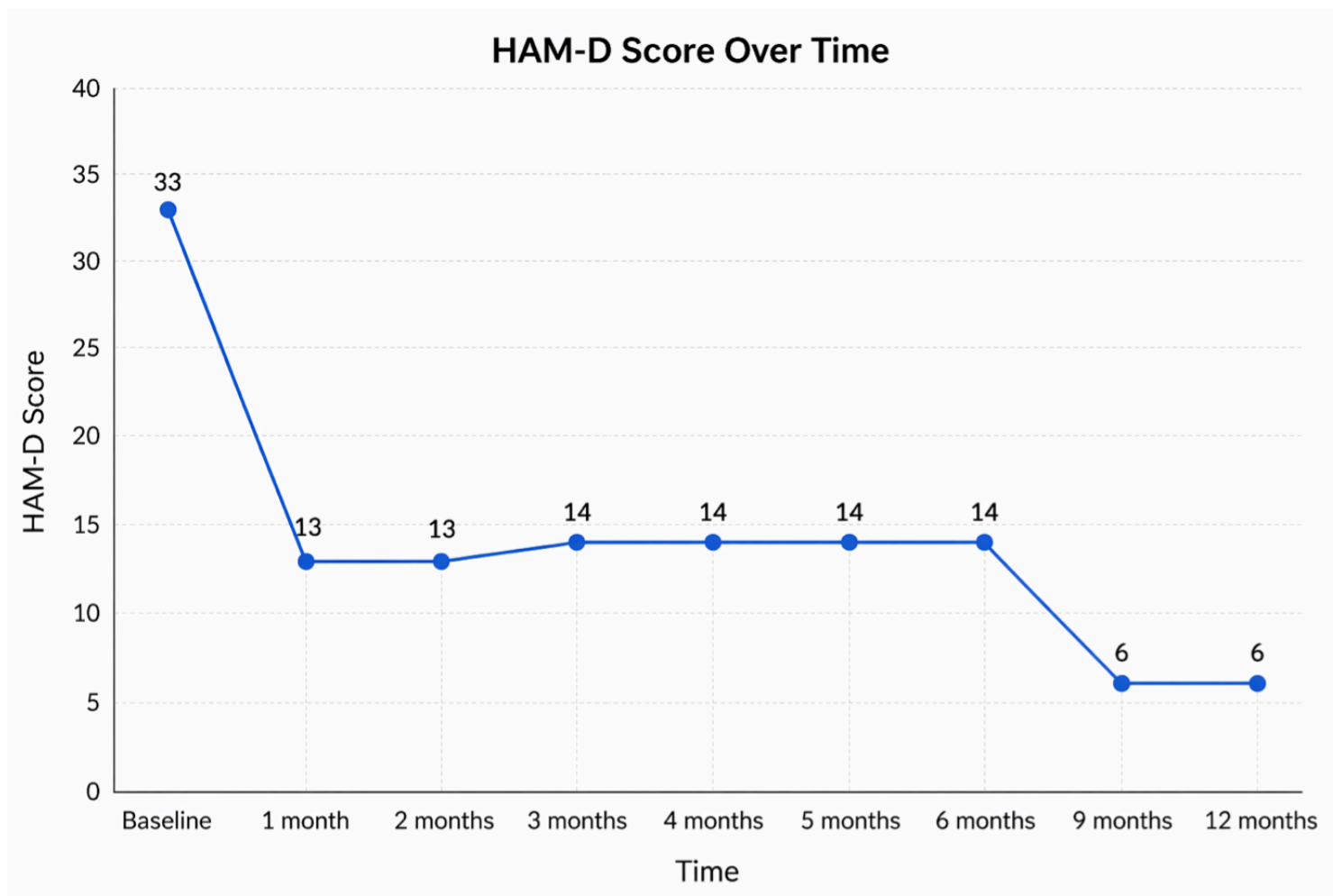


Figure 1

Trajectory of Hamilton Depression Rating Scale (HAM-D) (14) scores over 12 months of treatment with intranasal esketamine, showing a marked early reduction in symptom severity, stabilization during the intermediate phase, and subsequent achievement of remission.

Supplementary Files

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