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Intranasal esketamine as tool for rapid cycling bipolar disorder: A case report of successful mood stabilization

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ABSTRACT

Rapid Cyclic Bipolar Disorder (RCBD) is a debilitating condition that manifests as four or more episodes of depression, mania, or hypomania in a span of one year, with depression being the predominant event. RCBD is prevalent among individuals diagnosed with bipolar disorder and is associated with elevated suicide risk, prolonged disease duration, unfavorable clinical outcomes, and cognitive decline. The treatment of RCBD is challenging, owing to the poor response to lithium and other conventional treatments for bipolar disorder and the possibility of exacerbating rapid-cycling oscillations during depressive phases with the use of antidepressant therapies. Esketamine Nasal Spray (ESK-NS) has been approved for the treatment of Treatment-Resistant Depression but its application in the context of RCBD is limited and unknown. This study presents the case of a 56-year-old male diagnosed with RCBD who received ESK-NS treatment during a depressive episode and was followed up for 18 months. During the observation period, the subject exhibited a significant mood stabilization, with only a transient depressive episode observed during a three-month period of cessation of ESK-NS treatment, which promptly resolved upon reinstating ESK-NS therapy. Mild dissociative symptoms were observed during the initial doses of ESK-NS administration, but no other significant adverse events were reported. This case report provides initial evidence for the potential utilization of ESK-NS in the treatment of RCBD, supporting the hypothesis of an additional mood-stabilizing effect.

1. Introduction

Rapid cyclic bipolar disorder (RCBD) represents a severe condition characterized by four or more episodes of depression, mania, or hypomania within 1 year, with predominance of depressive events (McIntyre et al., 2022). RCBD is frequent among those affected by Bipolar Disorder and is associated with high suicidal risk, long disease duration, poor clinical outcome and cognitive impairment (McIntyre et al., 2022). Besides, RCBD management represents a challenging issue, characterized by poor response to lithium and other classic treatments for bipolar disorder (El-Mallakh et al., 2015). Furthermore, during depressive phases, the use of antidepressant therapies represents a great concern, since their risk of worsening rapid-cycling oscillations (El-Mallakh et al., 2015). Over the last years, Esketamine nasal spray (ESK-NS) has been approved by the European Medical Agency (EMA) as new therapeutic tool for Treatment-Resistant Depression (TRD), a clinical condition characterized by the absence of clinical response after two antidepressant trials, adequate for duration, dosage and compliance (Sforzini et al., 2022). ESK-NS innovative mechanism of action is related to a non-competitive antagonism of *N*-methyl-D-aspartate Receptor (NMDA-R), thus involving glutamatergic pathways. Several studies indicated the effectiveness and safety of ESK-NS in TRD, with rapid and sustained reduction of depressive symptoms (Wajs et al., 2020; Martinotti et al., 2022). Besides, ESK-NS seems to have a potential action in multiple condition, with preliminary findings indicating its effectiveness among subjects with comorbid substance use disorder (Chiappini et al., 2023), in elderly subjects (d'Andrea et al., 2023a,b), as well as in Obsessive-Compulsive Disorders (Martinotti et al., 2021). Nevertheless, ESK-NS possible use in bipolar subjects represents a challenging issue, due to the limited preliminary data supporting its safety and effectiveness in non-unipolar depressed subjects (Martinotti et al., 2023). However, according to EMA Summary of Product Characteristics (SPCs),

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ESK-NS use is not contraindicated in subject with BD, although a rigorous assessment of the risks and advantages of its usage in these patients is required.

To date, minimal knowledge exists regarding the potential utilization of ESK-NS in the context of RBCD and whether, similarly to other antidepressant compounds, it may result in an exacerbation of affective switches. Based on the evidence of glutamate dysregulation in RBCD pathophysiology (Michael et al., 2009; Veldic et al., 2019), we hypothesized an atypical, mood-stabilizing, antidepressant action of ESK-NS in these clinical conditions.

Herein, we report the case of a RCBD patient treated with ESK-NS during a depressive episode, followed-up for about 18 months, who obtained a stabilization of affective symptoms and an overall reduction of rapid cycling mood swings (Fig. 1).

2. Case presentation

This case concerns a 56 years-old Caucasian male, unemployed, widowed, admitted to the Mood Disorder outpatient unit at the Annunziata Hospital (Chieti, Italy) on February, 2021.

His familial history reveals that his mother had Bipolar Disorder Type II, while his sister was diagnosed with a schizoaffective disorder. On admission, the patient experienced the following symptoms: depressed mood, anhedonia, irritability, feeling of guilt, cognitive impairments (mainly concentration difficulties), sleep disturbances, high level of anxiety with concerns for the future and pessimistic thoughts, associated to suicidal ideation.

The disease onset occurred approximately 20 years before, initially as depressive episodes marked by low mood, anhedonia, social isolation, and hopelessness. Significantly, he lost his wife at age 41, a traumatic event that, by his account, intensified his depressive symptoms. In the past two years, he has undergone numerous depressive episodes, punctuated by hypomanic episodes characterized by euphoria, anxiety, restlessness, and hypersexuality. Depressive phases were often characterized by self-medication attempts through alcohol abuse and frequent episodes of binge drinking.

Notably, within the last year, he had two major depressive episodes and two hypomanic episodes, diagnosed based on DSM-5 criteria (Vahia, 2013). Furthermore, during the year prior to the admission, the patient had two hospitalizations in the psychiatric ward, due to the occurrence of suicidal ideation during the two aforementioned depressive episodes. Over the past two years, the escalating intensity and frequency of episodes, coupled with the onset of pronounced hypomanic episodes, have profoundly affected the patient's overall functioning. This deterioration has hindered his ability to perform regular work tasks, necessitating complete dependence on his daughter, who is his primary caregiver.

Previous therapies involved multiple lines of mood-stabilizers and antidepressants with slight response on the single episode but persistence of mood cycling (see Table 1). In addition, patient was treated during the last year by a qualified psychotherapist with one session/week of Cognitive Behavioral Therapy, without significant improvements of depressive symptoms. Given its clinical presentation and previous reported rapid mood cycling (i.e. four depressive/hypomanic episodes reported in the previous year), he received a diagnosis of Rapid Cycling Bipolar Disorder (RCBD), Type II, following DSM-V diagnostic criteria (Vahia, 2013).

The patient displayed no metabolic abnormalities and maintained good physical health, with a medical history free of significant conditions.

At the admittance time he was assuming the following therapy: Lithium Extended Release 600 mg/die, Lamotrigine 100 mg/die, Fluvoxamine 100 mg/die and Clonazepam 2,5 mg /die.

During psychiatric interview, severe distress and despair emerged. The patient underwent a thorough psychometric evaluation, reporting severe anxious and depressive symptoms (Montgomery Asberg

Table 1
Pharmacotherapies used.

Lithium	Partially effective/on going
Lamotrigine	Partially effective/on going
Bupropion	Ongoing
Fluvoxamine	Ineffective
Paroxetine	Ineffective
Quetiapine XR	Interrupted for sedation
Valproate	Interrupted for tremors

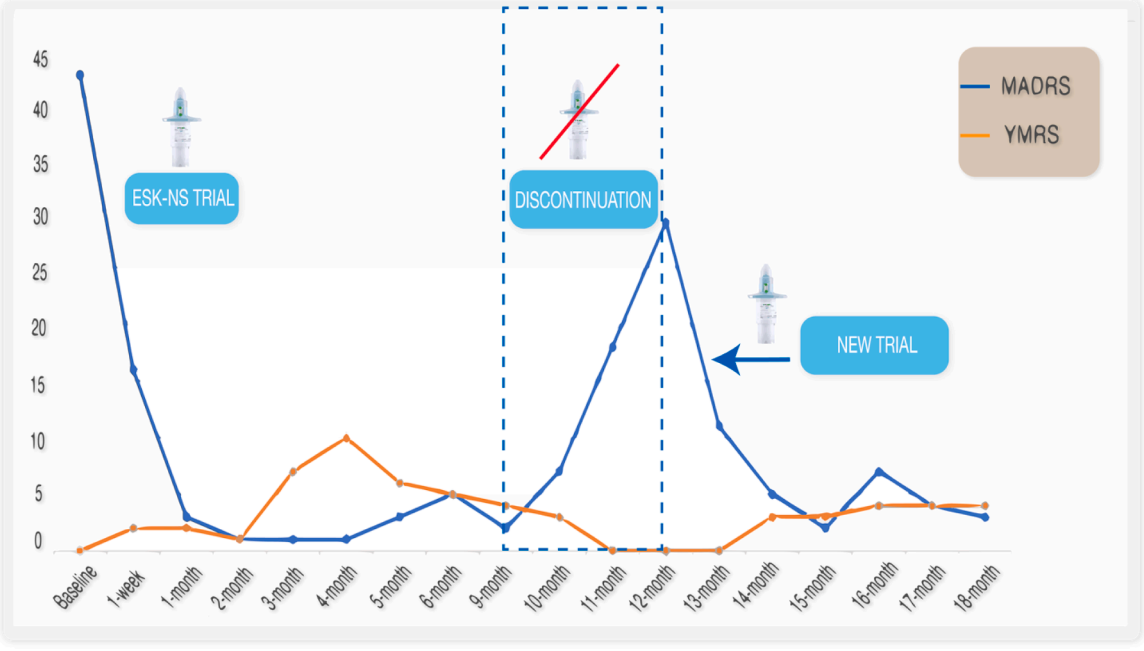

Fig. 1. Mood variations during all the observation period. ESK-NS discontinuation goes from month 9 until month 12.
Abbreviations: MADRS, Montgomery–Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale.

Depression Rating Scale score, 42; Hamilton Anxiety Scale, 31) without any manic symptoms (Young Mania Rating Scale, 0).

Given the condition of unstable depressive symptoms and inadequate response to previous therapies, patient was assigned to an ESK-NS nasal spray trial, which was started in August, 2021. During the first doses of ESK-NS administration, he presented mild dissociative symptoms, which quickly resolved. No other significant adverse events were observed. Dosage and treatment regimen are reported in Table 2.

Over the first treatment week, mood and anxious symptoms greatly improved, with remission from the depressive episode reached at the end of the first month and a stable euthymic state persisted for the following two months. During the third month, a slight mood elevation with sleep reduction and increased sexual interest, speech and irritability emerged (YMRS score: 7). Subsequently, ESK-NS therapeutic regimen was then reduced to one administration every two weeks and then one every month, reaching euthymic state during the following months, with an increase of subject's global functioning and its return to work. Patient remained stable until month 9 and ESK-NS therapy was discontinued.

Subsequently, three months after treatment discontinuation, he experienced a relapse in a severe depressive state, with decreased mood and energy, suicidal thoughts and sleeping difficulties associated with anxious distress (MADRS:29, HAM-A:24, YMRS:0). Despite several changes in therapy (antidepressant switch from Fluvoxamine to Bupropion hydrochloride 300 mg/die and Lamotrigine titrated up to 200 mg/die) symptoms persisted. A new trial with ESK-NS nasal spray was started on Month 12. After the second week, an increased in dosage was required due to a lack of clinical response. Subsequently, patient experienced a sustained euthymic state, with a significant well-being and remission of the depressive episode. ESK-NS treatment regimen was reduced to 56 mg, with one administration every two weeks. At month 18, 6 months from the beginning of the second trial, euthymic state appeared stable and no symptoms relapses were reported.

Table 2
Dosages and treatment sessions.

	Administration frequency	Dosage per session (mg)
1st month	2/weeks	56
2nd–5th month	1/week	56
6th–7th month	1 every two weeks	56
8th–9th month	1 every month	56
9th month–12th month	Treatment discontinued	
12th month	1/week	56
13th month–15th month	1/week	84
16th month–17th month	1/week	56
17th month–18th month	1 every two weeks	56

3. Discussion

To our knowledge, this is the first case reporting ESK-NS use in the treatment of rapid cycling bipolar disorder (RCBD). ESK-NS use in the treatment of RCBD has shown to be safe, without any observed affective switch and with improved results, leading to a sustained remission which was only disrupted during the period of ESK-NS withdrawal (between the 9th and 12th month) and promptly reinstated upon ESK-NS reintroduction.

There are multiple lines of evidence suggesting the potential use of ESK-NS as a pharmacotherapy in bipolar disorder: firstly, there have been several studies indicating a disruption of glutamatergic neurotransmission in individuals with bipolar disorder (Lener et al., 2017; Ehrlich et al., 2015); secondly, multiple studies have demonstrated the efficacy of intravenous ketamine in the treatment of bipolar depression (Bahji et al., 2022); thirdly, recent studies have indicated that the antidepressant action of ESK-NS may be related to the modulation of the tonic membrane flow of calcium and sodium (d'Andrea et al., 2023a,b), a mechanism of action shared by several mood stabilizers such as valproate (Zanatta et al., 2019), carbamazepine and lamotrigine (Sills and Rogawski, 2020). In accordance with these previous findings, the use of ESK-NS in this case showed efficacy not only in the treatment of the depressive episode, but also in providing satisfactory mood stabilization, disrupting the rapid cycling of mood. This resulted in an improvement in the overall functioning of the patient, including returning to work and a decrease in the number of hospitalizations (from two hospitalizations in the year prior to the introduction of ESK-NS, to no hospitalizations during the 18-month observation period following treatment introduction). Indeed, the absence of hospitalizations following ESK-NS introduction suggests the significant impact of this treatment on the natural course of the disease, leading to a reduction in healthcare costs associated with acute exacerbations, such as hospitalization costs or lost productivity, elements particularly relevant in the context of affective disorders (Greenberg et al., 2021).Moreover, a major advantage of this case report is the long follow-up period (18 months), during which sustained, stable mood improvements have been observed.

In conclusion, this case report preliminarily highlights the efficacy of ESK-NS not only as an antidepressant in the acute treatment of the depressive episode, but also in preventing long-term relapses and contributing to a proper mood stabilization. Further studies are needed to systematically evaluate the real long-term efficacy of ESK-NS as a treatment for bipolar disorder and RCBD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Bahji, A., Zarate, C.A., Vazquez, G.H., 2022. Efficacy and safety of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. Expert Opin. Drug Saf. 21 (6), 853–866. https://doi.org/10.1080/14740338.2022.2047928.

Chiappini, S., d'Andrea, G., De Filippis, S., Di Nicola, M., Andriola, I., Bassetti, R., Barlati, S., Pettorruso, M., Sensi, S., Clerici, M., Dell'Osso, B., Vita, A., Martinotti, G., 2023. Esketamine in treatment-resistant depression patients comorbid with substance-use disorder: a viewpoint on its safety and effectiveness in a subsample of patients from the REAL-ESK study. Eur. Neuropsychopharmacol. 74, 15–21. https://doi.org/10.1016/j.euroneuro.2023.04.011.

d'Andrea, G., Chiappini, S., McIntyre, R.S., Stefanelli, G., Carullo, R., Andriola, I., Zanardi, R., Martiadis, V., Sensi, S.L., Sani, G., Clerici, M., Lorenzo, G.Di, Vita, A., Pettorruso, M., Martinotti, G., 2023a. Investigating the effectiveness and tolerability of intranasal esketamine among older adults with treatment-resistant depression (TRD): a post-hoc analysis from the REAL-ESK study group. Am. J. Geriatr. Psychiatry. https://doi.org/10.1016/j.jagp.2023.06.016.

d'Andrea, G., Pettorruso, M., Lorenzo, G.Di, Mancusi, G., McIntyre, R.S., Martinotti, G, 2023b. Rethinking ketamine and esketamine action: are they antidepressants with mood-stabilizing properties?. In: Eur. Neuropsychopharmacol., 70, pp. 49–55. https://doi.org/10.1016/j.euroneuro.2023.02.010.

Ehrlich, A., Schubert, F., Pehrs, C., Gallinat, J., 2015. Alterations of cerebral glutamate in the euthymic state of patients with bipolar disorder. Psychiatry Res. 233 (2), 73–80. https://doi.org/10.1016/j.pscychresns.2015.05.010.

El-Mallakh, R.S., Vöhringer, P.A., Ostacher, M.M., Baldassano, C.F., Holtzman, N.S., Whitham, E.A., Thommi, S.B., Goodwin, F.K., Ghaemi, S.N., 2015. Antidepressants worsen rapid-cycling course in bipolar depression: a STEP-BD randomized clinical trial. J. Affect. Disord. 184, 318–321. https://doi.org/10.1016/j.jad.2015.04.054.

Greenberg, P.E., Fournier, A.-A., Sisitsky, T., Simes, M., Berman, R., Koenigsberg, S.H., Kessler, R.C., 2021. The economic burden of adults with major depressive disorder in the United States (2010 and 2018). Pharmacoeconomics 39 (6), 653–665. https://doi.org/10.1007/s40273-021-01019-4.

Lener, M.S., Niciu, M.J., Ballard, E.D., Park, M., Park, L.T., Nugent, A.C., Zarate, C.A.J., 2017. Glutamate and gamma-aminobutyric acid systems in the pathophysiology of major depression and antidepressant response to ketamine. Biol. Psychiatry 81 (10), 886–897. https://doi.org/10.1016/j.biopsych.2016.05.005.

Martinotti, G., Chiappini, S., Pettorruso, M., Mosca, A., Miuli, A., Di Carlo, F., D'Andrea, G., Collevecchio, R., Di Muzio, I., Sensi, S.L., Di Giannantonio, M., 2021. Therapeutic potentials of ketamine and esketamine in obsessive-compulsive disorder (OCD), substance use disorders (SUD) and eating disorders (ED): a review of the current literature. Brain Sci. 11 (7) https://doi.org/10.3390/brainsci11070856.

Martinotti, G., Dell'Osso, B., Di Lorenzo, G., Maina, G., Bertolino, A., Clerici, M., Barlati, S., Rosso, G., Di Nicola, M., Marcatili, M., D'Andrea, G., Cavallotto, C., Chiappini, S., De Filippis, S., Nicolò, G., De Fazio, P., Andriola, I., Zanardi, R., Nucifora, D., Di Mauro, S., Bassetti, R., Pettorruso, M., McIntyre, R.S., Sensi, S.L., di Giannantonio, M., Vita, A., Group, T.R.E.A.L.-E.S, 2023. Treating bipolar depression

with esketamine: safety and effectiveness data from a naturalistic multicentric study on esketamine in bipolar versus unipolar treatment-resistant depression. Bipolar Disord. https://doi.org/10.1111/bdi.13296. *n/a* (n/a).

Martinotti, G., Vita, A., Fagiolini, A., Maina, G., Bertolino, A., Dell'Osso, B., Siracusano, A., Clerici, M., Bellomo, A., Sani, G., d'Andrea, G., Chiaie, R.D., Conca, A., Barlati, S., Di Lorenzo, G., De Fazio, P., De Filippis, S., Nicolò, G., Rosso, G., Valchera, A., Nucifora, D., Di Mauro, S., Bassetti, R., Martiadis, V., Olivola, M., Belletti, S., Andriola, I., Di Nicola, M., Pettorruso, M., McIntyre, R.S., di Giannantonio, M., 2022. Real-world experience of esketamine use to manage treatment-resistant depression: a multicentric study on safety and effectiveness (REAL-ESK study). J. Affect. Disord. 319, 646–654. https://doi.org/10.1016/j.jad.2022.09.043.

McIntyre, R.S., Alda, M., Baldessarini, R.J., Bauer, M., Berk, M., Correll, C.U., Fagiolini, A., Fountoulakis, K., Frye, M.A., Grunze, H., Kessing, L.V., Miklowitz, D.J., Parker, G., Post, R.M., Swann, A.C., Suppes, T., Vieta, E., Young, A., Maj, M, 2022. The clinical characterization of the adult patient with bipolar disorder aimed at personalization of management. World Psychiatry 21 (3), 364–387. https://doi.org/10.1002/wps.20997.

Michael, N., Erfurth, A., Pfleiderer, B., 2009. Elevated metabolites within dorsolateral prefrontal cortex in rapid cycling bipolar disorder. Psychiatry Res. 172 (1), 78–81. https://doi.org/10.1016/j.pscychresns.2009.01.002.

Sforzini, L., Worrell, C., Kose, M., Anderson, I.M., Aouizerate, B., Arolt, V., Bauer, M., Baune, B.T., Blier, P., Cleare, A.J., Cowen, P.J., Dinan, T.G., Fagiolini, A., Ferrier, I. N., Hegerl, U., Krystal, A.D., Leboyer, M., McAllister-Williams, R.H., McIntyre, R.S., Meyer-Lindenberg, A., Miller, A.H., Nemeroff, C.B., Normann, C., Nutt, D., Pallanti, S., Pani, L., Penninx, B.W.J.H., Schatzberg, A.F., Shelton, R.C., Yatham, L. N., Young, A.H., Zahn, R., Aislaitner, G., Butlen-Ducuing, F., Fletcher, C., Haberkamp, M., Laughren, T., Mäntylä, F.-L., Schruers, K., Thomson, A., Arteaga-Henríquez, G., Benedetti, F., Cash-Gibson, L., Chae, W.R., De Smedt, H., Gold, S.M., Hoogendijk, W.J.G., Mondragón, V.J., Maron, E., Martynowicz, J., Melloni, E., Otte, C., Perez-Fuentes, G., Poletti, S., Schmidt, M.E., van de Ketterij, E., Woo, K., Flossbach, Y., Ramos-Quiroga, J.A., Savitz, A.J., Pariante, C.M., 2022. A delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials. Mol. Psychiatry 27 (3), 1286–1299. https://doi.org/10.1038/s41380-021-01381-x.

Sills, G.J., Rogawski, M.A., 2020. Mechanisms of action of currently used antiseizure drugs. Neuropharmacology 168, 107966. https://doi.org/10.1016/j.neuropharm.2020.107966.

Vahia, V.N., 2013. Diagnostic and statistical manual of mental disorders 5: a quick glance. Indian J. Psychiatry 55 (3), 220–223. https://doi.org/10.4103/0019-5545.117131.

Veldic, M., Millischer, V., Port, J.D., Ho, A.M.-C., Jia, Y.-F., Geske, J.R., Biernacka, J.M., Backlund, L., McElroy, S.L., Bond, D.J., Villaescusa, J.C., Skime, M., Choi, D.-S., Lavebratt, C., Schalling, M., Frye, M.A, 2019. Genetic variant in SLC1A2 is associated with elevated anterior cingulate cortex glutamate and lifetime history of rapid cycling. Transl. Psychiatry 9 (1), 149. https://doi.org/10.1038/s41398-019-0483-9.

Wajs, E., Aluisio, L., Holder, R., Daly, E.J., Lane, R., Lim, P., George, J.E., Morrison, R.L., Sanacora, G., Young, A.H., Kasper, S., Sulaiman, A.H., Li, C.-T., Paik, J.-W., Manji, H., Hough, D., Grunfeld, J., Jeon, H.J., Wilkinson, S.T., Drevets, W.C., Singh, J.B., 2020. 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 (3), 81. https://doi.org/10.4088/JCP.19m12891.

Zanatta, G., Sula, A., Miles, A.J., Ng, L.C.T., Torella, R., Pryde, D.C., DeCaen, P.G., Wallace, B.A., 2019. Valproic acid interactions with the NavMs voltage-gated sodium channel. Proc. Natl. Acad. Sci. USA 116 (52), 26549–26554. https://doi.org/10.1073/pnas.1909696116.