

INTRANASAL ESKETAMINE AND MAOI COMBINATION IN THE MANAGEMENT OF TREATMENT-RESISTANT DEPRESSION: A CASE REPORT

ASSOCIAÇÃO DE ESCETAMINA INTRANASAL E INIBIDOR DA MONOAMINOXIDASE (IMAO) NO MANEJO DA DEPRESSÃO RESISTENTE: RELATO DE CASO

ASOCIACIÓN DE ESKETAMINA INTRANASAL E INHIBIDOR DE LA MONOAMINOXIDASA (IMAO) EN EL TRATAMIENTO DE LA DEPRESIÓN RESISTENTE AL TRATAMIENTO: INFORME DE UN CASO



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ABSTRACT

Introduction: Treatment-resistant depression (TRD) represents a significant clinical challenge, particularly when associated with suicidal ideation. Intranasal esketamine has emerged as an effective therapeutic option in refractory cases, while monoamine oxidase inhibitors (MAOIs) remain relevant in the management of severe and resistant conditions.

Objective: To describe the clinical course of a patient with TRD treated with the combination of intranasal esketamine and tranylcypromine.

Method: Case report of a 27-year-old female patient diagnosed with recurrent depressive disorder and a history of therapeutic failure to multiple classes of antidepressants, mood stabilizers, and antipsychotics, followed through clinical evaluation and standardized rating scales (HAM-A and MADRS).

Results: After initiation of the combined treatment, a rapid and sustained clinical improvement was observed, with significant reduction of depressive and anxiety symptoms, as well as remission of suicidal ideation. The treatment was well tolerated, with no relevant adverse events.

Conclusion: The association of intranasal esketamine and a MAOI proved to be effective and safe in this case of TRD, suggesting that it may represent a viable therapeutic alternative in selected situations, provided that strict clinical monitoring is ensured.

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Keywords: Depressive Disorder. Treatment-Resistant Esketamine. Monoamine Oxidase Inhibitors.

RESUMO

Introdução: O transtorno depressivo resistente ao tratamento (TDR) representa um desafio clínico significativo, especialmente quando associado à ideação suicida. A escetamina intranasal tem emergido como uma opção terapêutica eficaz em casos refratários, enquanto os inibidores da monoaminooxidase (IMAO) permanecem relevantes no manejo de quadros graves e resistentes.

Objetivo: Descrever a evolução clínica de uma paciente com TDR submetida à associação de escetamina intranasal e tranilcipromina.

Método: Relato de caso de paciente do sexo feminino, 27 anos, com diagnóstico de transtorno depressivo recorrente e histórico de falha terapêutica a múltiplas classes de antidepressivos, estabilizadores de humor e antipsicóticos, acompanhada por avaliação clínica e escalas padronizadas (HAM-A e MADRS).

Resultados: Após a introdução do tratamento combinado, observou-se melhora clínica rápida e sustentada, com redução significativa dos sintomas depressivos e ansiosos, além de remissão da ideação suicida. O tratamento foi bem tolerado, sem ocorrência de eventos adversos relevantes.

Conclusão: A associação de escetamina intranasal e IMAO mostrou-se eficaz e segura neste caso de TDR, sugerindo ser uma alternativa terapêutica viável em situações selecionadas, desde que realizada sob monitoramento clínico rigoroso.

Palavras-chave: Depressão Resistente ao Tratamento. Escetamina. Inibidores da Monoaminooxidase.

RESUMEN

Introducción: La depresión resistente al tratamiento (TDR) representa un desafío clínico significativo, especialmente cuando se asocia con ideación suicida. La escetamina intranasal ha surgido como una opción terapéutica eficaz en casos refractarios, mientras que los inhibidores de la monoaminooxidasa (IMAO) siguen siendo relevantes en el manejo de cuadros graves y resistentes.

Objetivo: Describir la evolución clínica de una paciente con TDR sometida a la asociación de escetamina intranasal y tranilcipromina.

Método: Reporte de caso de una paciente de sexo femenino, de 27 años, con diagnóstico de trastorno depresivo recurrente y antecedentes de fracaso terapéutico a múltiples clases de antidepressivos, estabilizadores del estado de ánimo y antipsicóticos, acompañada mediante evaluación clínica y escalas estandarizadas (HAM-A y MADRS).

Resultados: Tras la introducción del tratamiento combinado, se observó una mejoría clínica rápida y sostenida, con reducción significativa de los síntomas depresivos y ansiosos, además de remisión de la ideación suicida. El tratamiento fue bien tolerado, sin eventos adversos relevantes.

Conclusión: La asociación de escetamina intranasal e IMAO resultó eficaz y segura en este caso de TDR, lo que sugiere que puede constituir una alternativa terapéutica viable en situaciones seleccionadas, siempre que se realice bajo un monitoreo clínico riguroso.



Palabras clave: Depresión Resistente al Tratamiento. Escetamina. Inhibidores de la Monoaminooxidasa.

1 INTRODUCTION

Major depressive disorder (MDD) is a psychiatric condition defined by the presence of at least five symptoms over a period of at least two weeks, and the presence of depressed mood and/or loss of interest or pleasure (anhedonia) is mandatory, according to the diagnostic criteria established by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). These additional symptoms may include changes in appetite or weight, sleep disturbances, fatigue, feelings of worthlessness or excessive guilt, difficulty concentrating, and recurring thoughts of death or suicide. A precise understanding of these criteria is essential, especially when considering emerging therapeutic interventions, such as intranasal esketamine, which has an approved indication for cases of MDD with acute suicidal ideation, reinforcing the need for careful and individualized clinical evaluation in these contexts ¹.

This disorder significantly impacts the quality of life and daily functioning of individuals, in addition to being associated with a high mortality rate. It is estimated that between 10% and 20% of patients with MDD attempt suicide in their lifetime, and life expectancy can be reduced by up to 10 years. Despite the widespread availability of antidepressant treatments, therapeutic response is still a challenge: only one-third of patients achieve remission with first-line treatment, while another third develop treatment-resistant depression (RDT) ².

Treatment-resistant depression (RDT) represents a major challenge in clinical practice, especially when accompanied by suicidal ideation. In this context, intranasal esketamine, ketamine's S-enantiomer, an N-methyl-D-aspartate (NMDA) receptor antagonist, has stood out as a promising therapeutic option, especially when used in association with conventional antidepressants ^{3,4}. Its mechanism of action involves modulating glutamate neurotransmission, promoting increased neurotrophic factor release and stimulating synaptogenesis. Unlike antidepressants that act on the monoaminergic system, esketamine exerts its antidepressant effect through a distinct primary pathway, which contributes to its relevance in the management of RDT ^{5,6}.

Monoamine oxidase inhibitors (MAOIs), irreversible and non-selective drugs, were the first to be used in the treatment of depression, preceding the discovery of tricyclic antidepressants in the 1950s and the emergence of other therapeutic classes in the following decades. Initially, MAOIs were the main option for patients with atypical depression, characterized by symptoms such as phobic anxiety, hyperphagia, hypersomnia, and mood reactivity. However, despite studies suggesting similar efficacy among different classes of antidepressants in the treatment of major depressive disorder, the use of MAOIs has become less frequent due to dietary restrictions and drug interactions associated with their use,

impacting their acceptability and tolerability. Currently, these drugs are generally indicated for cases of treatment-resistant depression ^{7,8}.

We report the case of a patient with severe RDT who showed significant improvement after the introduction of intranasal esketamine combined with tranylcypromine, a monoamine oxidase inhibitor (MAOI), highlighting the synergy of this approach in the management of a complex clinical picture.

2 CLINICAL CASE

A 27-year-old female patient has been under psychiatric follow-up since 2015, with a diagnosis of recurrent depressive disorder. Throughout the evolution, she was submitted to multiple psychopharmacological strategies, including antidepressants of different classes (selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and atypical antidepressants), mood stabilizers, atypical antipsychotics, as well as hypnotics, anxiolytics, and psychostimulants. All medications were administered in therapeutic doses and for periods considered adequate, according to current clinical guidelines. Despite the interventions performed, there was no satisfactory clinical response, characterizing treatment-resistant depression.

In January 2023, she started a new psychiatric follow-up in a severe depressive episode, presenting persistent depressed mood (hypothymia), intense anxiety, a feeling of helplessness, and recurrent suicidal ideation. In the initial evaluation, high scores were observed on the Hamilton Anxiety Rating Scale (HAM-A: 24 points) and Montgomery–Åsberg Depression Rating Scale (MADRS: 33 points). Pharmacological treatment with paroxetine (25 mg/night) was instituted, associated with the recommendation of psychotherapy.

Despite the initial improvement observed in February 2023, the patient presented a progressive worsening of the clinical condition in subsequent consultations, evidenced by the increase in the scores on the evaluation scales (Figure 1), even after therapeutic adjustments, including increasing the dose of paroxetine to 50 mg/night and potentiation with brexpiprazole (2 mg/night), in addition to strengthening adherence to psychotherapy.

In September 2023, in view of the worsening of symptoms and intensification of suicidal ideation, with HAM-A scores of 28 and MADRS of 43, it was decided to change the drug regimen to tranylcypromine (60 mg/day), associated with quetiapine (25 mg/night), and authorization was requested to start treatment with intranasal esketamine, considering the diagnosis of recurrent depressive disorder in a severe episode, resistant to pharmacological treatment, associated with recurrent suicidal ideation.

The authorization for the use of intranasal esketamine was granted in December 2023. The patient underwent the standard therapeutic protocol, consisting of two weekly applications for four weeks (84 mg per application), followed by a weekly application for four weeks, and then fortnightly applications for four months, with the end of the maintenance phase in May 2024. Throughout the protocol, the patient maintained regular use of tranylcypromine (60 mg/day) and showed good adherence to psychotherapy. The association was well tolerated, with no occurrence of significant adverse events.

After the start of combined treatment, rapid and sustained clinical improvement was observed, with a significant reduction in depressive and anxious symptoms, in addition to complete remission of suicidal ideation. The scores on the HAM-A and MADRS scales progressively decreased, reaching 9 points in both at the end of the treatment. In January 2024, after the second month of esketamine use, the patient already had a substantial clinical response, with stability of the condition and important functional improvement.

The patient fully complied with the intranasal esketamine protocol and, at the end of treatment, was clinically stable, with no need to restart the medication. Currently, he remains under regular psychiatric follow-up, using tranylcypromine (60 mg/day), with periodic clinical monitoring to assess the maintenance of the therapeutic response.

3 DISCUSSION

This case report highlights the efficacy of intranasal esketamine as part of a combination therapeutic strategy in the management of treatment-resistant depressive disorder (RDT), particularly in a context of high suicide risk. The association with tranylcypromine proved to be a promising alternative, possibly due to the synergistic effect between the modulation of the glutamatergic system promoted by esketamine and the increase in the levels of monoaminergic neurotransmitters resulting from the inhibition of monoamine oxidase.⁹

The efficacy and safety of intranasal esketamine have already been demonstrated in randomized controlled trials, such as the ASPIRE I and II studies, which evaluated patients with resistant depression associated with acute suicidal ideation. These studies showed a significant reduction in depression scores in the first 24 hours after administration, in addition to a favorable tolerability profile^{6,10}. Recent systematic reviews reinforce these findings, highlighting the rapid antidepressant action of esketamine when compared to conventional antidepressants, especially as an adjuvant therapy in cases of RDT¹¹.

On the other hand, monoamine oxidase inhibitors, although currently less used due to dietary restrictions and the potential for drug interactions, remain a relevant therapeutic option

in severe and refractory depressive conditions. The combination of intranasal esketamine with MAOIs, such as tranylcypromine, is still little explored in the literature, especially in controlled studies, which makes the present report clinically relevant. In this case, the association was well tolerated and was not associated with serious adverse events, possibly due to the rigorous clinical monitoring and multidisciplinary approach adopted.

The observed clinical response reinforces the importance of therapeutic individualization in patients with RDT, especially in those who do not have a satisfactory response to conventional strategies. In complex clinical scenarios, such as the one described, combined approaches can be fundamental to achieve symptomatic remission and suicide risk reduction, expanding the therapeutic possibilities available for the management of RDT.

4 CONCLUSION

The association of intranasal esketamine with tranylcypromine proved to be effective in the management of a case of severe treatment-resistant depressive disorder (RDT) in a patient with a history of refractoriness to multiple therapeutic approaches. Significant clinical improvement in depressive and anxious symptoms was observed, as well as a substantial reduction in suicidal risk. Although still little explored in the literature, the pharmacological combination was well tolerated in this case, with no occurrence of relevant adverse events, reinforcing its clinical viability when conducted under close monitoring.

This report highlights the importance of combined and individualized therapeutic strategies in the management of RDT, especially in complex clinical contexts, in which conventional approaches alone are insufficient. Continuous follow-up and periodic reassessment of the need to maintain treatment remain essential to sustain the clinical benefits achieved.

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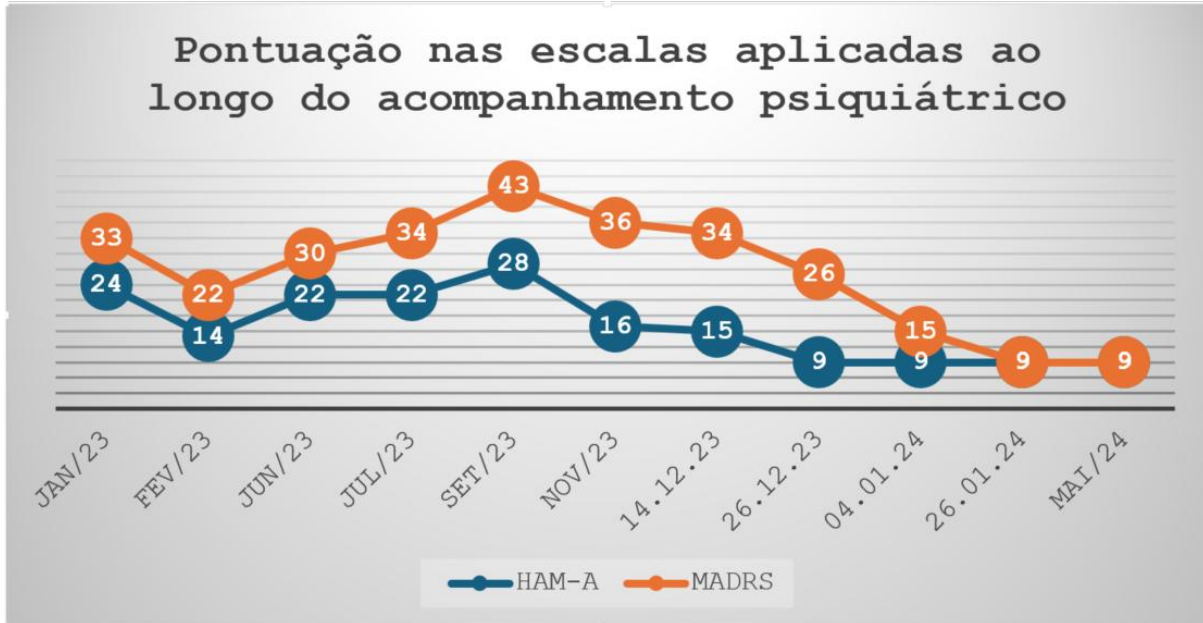
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ANNEX

Figure 1

Longitudinal evolution of Hamilton Anxiety Rating Scale (HAM-A) and Montgomery–Åsberg Depression Rating Scale (MADRS) scores during combination treatment with tranylcypromine and intranasal esketamine



Source: Authors.