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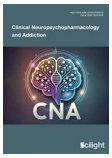

Case Report

Esketamine in Geriatric Depression and Pseudodementia: A Case Study

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Abstract: Geriatric depression is often accompanied by cognitive decline, complicating its diagnosis and treatment. In elderly patients, distinguishing between primary neurodegenerative disorders and depressive pseudodementia remains a major clinical challenge. Esketamine, a rapid-acting N-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a promising treatment for treatment-resistant depression (TRD), with the potential to improve cognitive function. We describe the case of a 79-year-old female patient with a long-standing history of major depressive disorder (MDD) who presented with a moderate-to-severe depressive episode unresponsive to multiple antidepressant treatments. The patient exhibited significant cognitive impairment, raising concerns about underlying neurodegenerative pathology. A comprehensive clinical and neurocognitive evaluation suggested depressive pseudodementia rather than primary dementia. Given her treatment resistance, intranasal esketamine was administered as an adjunctive therapy. Over six months, the esketamine treatment significantly decreased depressive symptoms, as indicated by MADRS, HAMD-21, and HAM-A scores. Cognitive assessments (MMSE and MoCA) showed notable improvements, supporting the hypothesis that effective depression treatment can reverse cognitive deficits associated with pseudodementia. Esketamine was well-tolerated, with minimal side effects, including a transient hypertensive episode that was managed conservatively. This case highlights esketamine's potential to treat severe depression and the associated pseudodementia in elderly patients. Its rapid onset of action, favorable safety profile, and ability to improve cognitive performance suggest it may be a viable alternative to electroconvulsive therapy (ECT) for geriatric TRD. Further research is needed to evaluate the long-term outcomes and optimize treatment strategies for this complex population.

Keywords: esketamine; geriatric depression; pseudodementia; treatment-resistant depression; cognitive function; neuroplasticity

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1. Introduction

Depression represents a significant global public health challenge [1], with its complexity exacerbated in the elderly by the presence of concurrent cognitive decline, which complicates its diagnosis and treatment [2]. Geriatric depression is characterized by pervasive despair, social withdrawal, and anhedonia, frequently co-occurring with cognitive deficits, thus creating a complex clinical scenario [3]. Recently, esketamine has emerged as a promising treatment for psychiatric disorders, making it a potential drug for patients presenting with depression, aging, and cognitive impairment symptoms [4].

Esketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that can control depression, particularly in individuals with cognitive impairment. By modulating glutamatergic neurotransmission and enhancing synaptic plasticity, esketamine may target the neurodegenerative mechanisms underlying both depression and cognitive decline. Its rapid onset of action and potential to alleviate suicidal ideation further underscore its utility for urgent interventions [5].

In this manuscript, we present a case study of a 79-year-old patient who experienced a moderate-to-severe depressive episode unresponsive to conventional antidepressant therapy. This case underscores the significant benefits of esketamine treatment, with a particular emphasis on its potential to improve cognitive performance. It provides evidence supporting the ability of esketamine to address "depressive pseudodementia," a condition where cognitive deficits stem from depression rather than primary neurodegenerative processes. Depressive pseudodementia can closely resemble true dementia due to overlapping symptoms such as memory loss, disorientation, and impaired concentration, but it remains distinct as it is reversible with effective treatment of the underlying depression [4].

2. Case Description

A 79-year-old female patient with a diagnosis of MDD presented to our center with a current episode of moderate-to-severe severity. Her psychiatric family history includes a positive association with depression, including a brother who died by suicide. The patient, married with two children and several grandchildren, had consistently cared for her family. Formerly a specialized nurse, she is now retired. Her first depressive episode occurred over 15 years ago and exhibited similar symptoms to the current episode, including cognitive decline, concentration difficulties, fatigue, abulia, anhedonia, increased social withdrawal, diminished interest in significant activities, labile mood, and heightened anxiety. This initial episode was prolonged and required significant time to achieve complete remission.

The patient was referred by her community psychiatrist due to persistent, nonspecific, treatment-resistant depressive symptoms that had not improved despite three lines of treatment.

The first-line treatment consisted of duloxetine (90 mg) from September 2021 to May 2022. Due to insufficient response, therapy was switched to sertraline (200 mg) in May. Subsequently, an augmentation strategy was implemented with quetiapine (150 mg) from July 2022 to December 2022; however, no significant clinical improvement was observed despite good adherence.

Given the persistent symptoms, a third-line approach was attempted with fluoxetine (titrated to 40 mg) in combination with lithium carbonate (900 mg) from December 2022 to May 2023, but this regimen also failed to achieve a satisfactory therapeutic response. Since December 2023, lithium has been discontinued and replaced with olanzapine Table 1 (Treatment Timeline).

Table 1 Treatment Timeline

Time Period	Medication and Dosage	Clinical Notes
September 2021–May 2022	Duloxetine 90 mg	No response
May 2022–July 2022	Sertralina 200 mg	No response
July 2022–December 2022	Sertraline 200 mg + Quetiapine 150 mg RP	No response
December 2022–May 2023	Fluoxetine up to 40 mg + Lithium 900 mg	No response
May 2023–December 2023	Fluoxetine 40 mg + Olanzapina 2,5 mg	No response
December 2023	Esketamine 28 mg + Fluoxetine 40 mg + Olanzapine 2,5 mg	Start Esketamine
January 2024	Esketamine 56 mg + Fluoxetine 40 mg	Good Response
February 2024–June 2024	Esketamine 28 mg + Fluoxetine 40 mg + Trazodone 75 mg RP	Remission
July 2024–January 2025	Fluoxetine 40 mg + Trazodone 75 mg RP	Sustained remission

Imaging evaluations included a brain CT scan in 2021, which was normal, and a repeat CT scan in 2022 as recommended by a neurologist. The 2022 scan reported: "fourth ventricle of regular dimensions and morphology, in place. Supratentorial ventricular system within normal limits, symmetric. Minimal widening of cortical sulci predominantly at the vertex; cranial base cisterns are within normal limits. Midline structures are in alignment. Regular position of cerebellar tonsils. Parietal calcifications of the carotid siphons. Mucous stagnation in the right sphenoid sinus and minimally in the homolateral mastoid".

Neurocognitive tests and neurological evaluation indicated a modest, multifactorial cognitive decline that did not progress in a manner consistent with typical dementia. Consequently, the patient was referred for a new psychiatric evaluation to differentiate between moderate cognitive decline and depressive pseudodementia.

3. Diagnostic Assessment

During the initial consultation, the patient presented with considerable anxiety and struggled to engage in conversation, providing only brief responses to direct questions. Oro-buccal dyskinesia was prominently observed, likely attributable to antidepressant-related side effects, although such manifestations remain rare. Given the patient's evident distress and communication difficulties, her daughter was interviewed to obtain a more comprehensive medical history. The daughter reported a recent clinical decline, characterized by significant deterioration in cognitive and motor functions, social withdrawal and the abandonment of previously enjoyed activities such as driving, household management, cooking, and childcare. Additionally, the patient exhibited noticeable changes in sleep patterns and reduced food intake. This episode had persisted for approximately two years.

A thorough differential diagnosis was conducted to distinguish between senile dementia and depressive pseudodementia. The diagnosis suggested the existence of depressive pseudodementia due to the sudden onset and rapid progression, coupled with non-specific memory disturbances, global verbal impairments, persistent depressed mood without significant nocturnal variations, vegetative symptoms, and the patient's prior psychiatric history.

Given the patient's history and the inadequate response to multiple antidepressants treatment, intranasal esketamine was introduced following pharmaceutical protocols.

The study spanned 6 months, during which comprehensive clinical data, including medical history and psychometric evaluations (MADRS, HAMD-21, HAM-A for depression and anxiety) and cognitive assessments (MMSE and MoCA), were collected at five intervals: baseline (T0), one week (T1), one month (T2), three months (T3), and six months (T4). The patient, diagnosed with TRD and a severe depressive episode, had a MADRS score of 42 and an MMSE score of 16 out of 30 (Figure 1).

Throughout the 6-month study, the patient received intranasal esketamine as an adjunct to her ongoing treatment (Fluoxetine and Olanzapine), administered in accordance with Italian Medicines Agency (AIFA) guidelines. The aim was to evaluate esketamine's efficacy in addressing both depression and cognitive impairment. Throughout the six-month study, the patient received intranasal esketamine as an adjunct to fluoxetine and olanzapine, administered per Italian Medicines Agency (AIFA) guidelines.

Preliminary results indicated a rapid and significant reduction in depressive symptoms, as evidenced by improvements in MADRS, HAMD-21, and HAM-A scores from the one-month assessment (T2) through to the three-month (T3) and six-month follow-ups (T4). Cognitive assessments also revealed significant improvements in MMSE and MoCA scores, suggesting a potential link between depressive symptom reduction and cognitive recovery (Figure 2).

Overall, side effects were minimal, with a single incident of elevated blood pressure occurring around the second month, which was managed with clonidine. Additionally, a mild, transient motor slowing effect, lasting approximately two hours, was observed primarily during the first month of treatment.

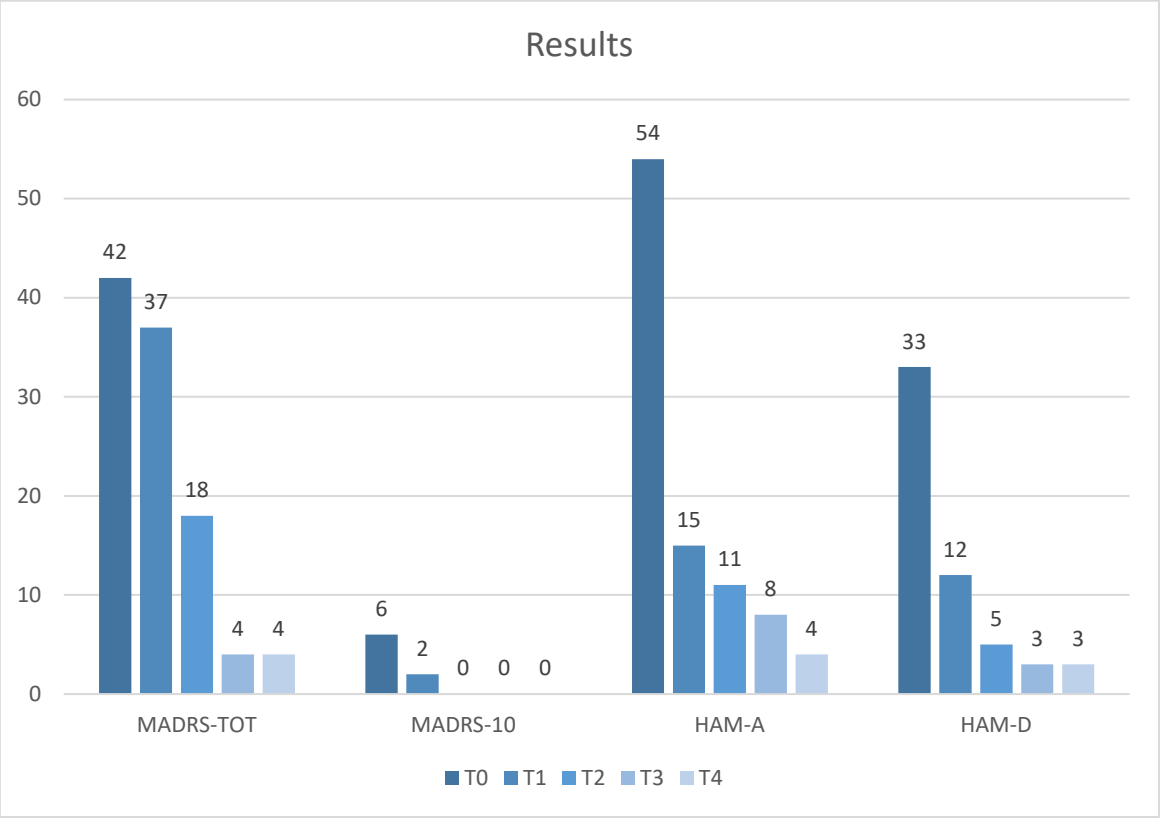

Figure 1. Interviews scores in different time points

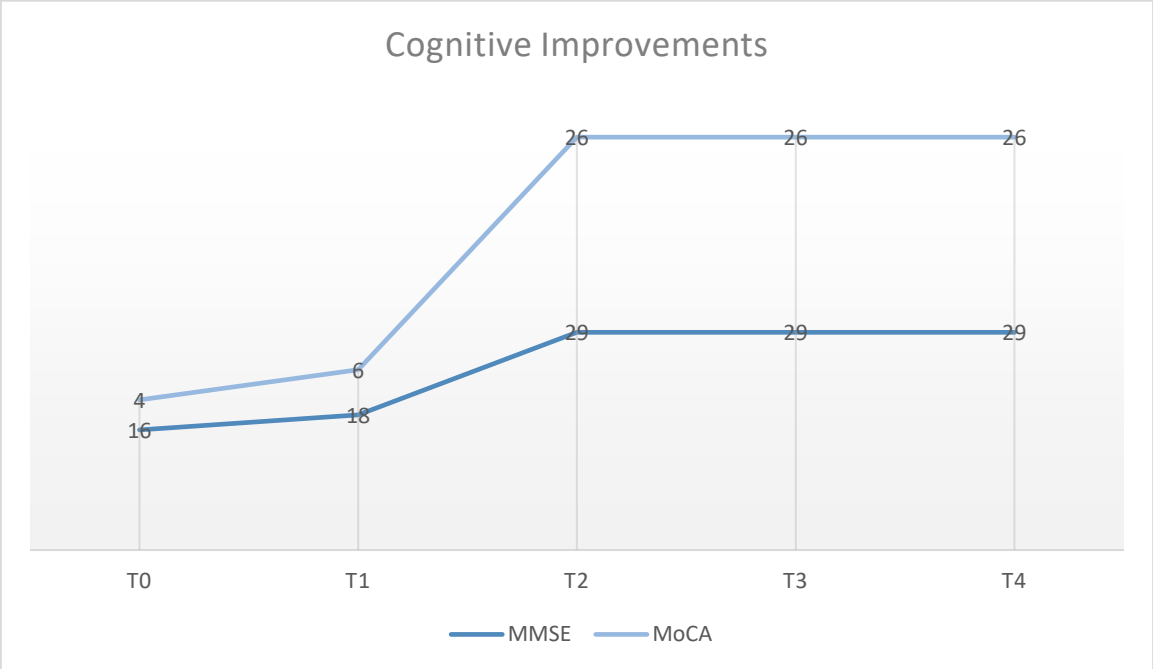

Figure 2. cognitive scores in different timelines

4. Discussion

The management of TRD in elderly patients is particularly challenging due to the increased clinical complexity arising from comorbid medical conditions and preexisting cognitive impairments. Esketamine is a promising treatment option for this population, given its rapid onset of action and ability to significantly reduce depressive symptoms [6]. However, assessing its impact on cognitive function in elderly patients remains crucial. Preliminary studies suggest that esketamine not only alleviates depressive symptoms but may also enhance cognitive domains such as attention and memory. Further research is needed to fully understand the long-term effects and safety profile of esketamine in elderly patients with TRD.

This case study highlights esketamine's potential benefits in simultaneously improving depressive symptoms and cognitive function.

Prior to this intervention, the patient had undergone multiple antidepressant treatments with minimal or no improvement. Esketamine therapy caused a rapid reduction in depressive symptoms, restoring mood and reducing anxiety, ultimately enhancing the patient's quality of life. Neurocognitive assessments confirmed that the treatment improved cognitive function, reinforcing the hypothesis that effective depression treatment can positively influence cognitive performance.

This clinical case highlights the need for further research to clarify the long-term effects of intranasal esketamine in elderly patients with TRD. The efficacy and safety of this treatment approach warrant more extensive investigation. Nonetheless, the positive outcomes observed suggest that esketamine may hold promise for future use in elderly patients with multiple comorbidities and symptoms of depressive pseudodementia.

5. Conclusions

Further research is essential to fully understand the mechanisms behind esketamine's effect on depression and cognitive function. This case highlights esketamine potential as a valuable treatment option for geriatric patients with TRD and cognitive impairments. The rapid improvement observed in both depressive symptoms and cognitive performance highlights its promise in addressing the complex interplay between depression and cognitive decline.

Esketamine can prevent neurodegenerative processes by targeting neuroplasticity and glutamatergic neurotransmission. Further research is essential to elucidate its long-term efficacy and safety profile. The management of TRD in older adults is further complicated by the higher prevalence of medical comorbidities and the potential complications associated with them. Traditionally, ECT has been considered a therapeutic choice for this population, despite concerns about side effects, particularly in the presence of comorbidities. Recent studies suggest that esketamine may represent a promising alternative to ECT for elderly patients with TRD. When strict exclusion criteria are followed, the side effects of esketamine in older adults appear comparable to those observed in younger patients, making it a viable therapeutic option in this complex population.

Additionally, esketamine has the advantage of being a less-invasive administration with rapid onset of antidepressant effects, making it particularly useful in older adults with comorbidities that may increase the risks associated with ECT. However, further studies are essential to evaluate the long-term efficacy and safety profile of esketamine in this population, in order to determine its optimal role in the treatment of TRD in the elderly.

Author Contributions

F.M.: conceptualization, methodology, writing; G.C.M.: data curation, writing; A.G.: visualization, investigation; V.M.: supervision; B.M.D.: software, validation, supervision; N.B.: writing—reviewing and editing; M.O.: conceptualitation, data curation, writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Pavia Ethics Commitee during its session on 27 August 2021 (opinion no. 84157/21) with a subsequent amendment issued under no. 0102231/21.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data supporting the findings of this study are available upon reasonable request from the corresponding author. Due to ethical and privacy considerations, some data cannot be shared publicly. However, de-identified data may be made available to qualified researchers upon request, in accordance with institutional and legal guidelines.

Conflicts of Interest

The authors declare no conflict of interest.

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