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When Mood and Time Align: Nasal Esketamine Reduces Lived Time Disturbances in Treatment-Resistant Depression

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Abstract: These two cases highlight the utility of a focused, structured clinical phenomenological interview in measuring treatment effectiveness in subjective experience. Two male patients, aged 35 and 27, of Serbian ethnicity with treatment-resistant depression were treated with nasal esketamine, with clinical progress monitored using both the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Transdiagnostic Assessment of Temporal Experience (TATE), a structured instrument assessing the patient's felt sense of time. Notably, TATE scores in the first case reached general population levels at week 4, one week prior to the treatment response, as indicated by MADRS. These findings underscore the value of phenomenological assessments in complementing traditional depression scales to capture nuanced improvements during treatment.

Introduction

Treatment-resistant depression (TRD) presents a substantial clinical challenge. Nasal esketamine is a rapidly-acting option for patients who fail to respond to multiple standard treatments. While its ability to alleviate core depressive symptoms is well-established, much less is known about its influence on patients' lived experiences, including the felt sense of time – a key feature of depression that contributes to a sense of stagnation, hopelessness, and disconnection[1,2]. Moreover, capturing the phenomenal nuances of experience is challenging as they are often not self-reported. Importantly, the prevalence of negative affective states in the Serbian population is estimated at 5.7%[3].

Transdiagnostic Assessment of Temporal Experience (TATE) is a validated, front-loaded structured phenomenological instrument developed to quantify these nuances regarding time[4,5]. In this paper, we describe two cases of male patients with treatment-resistant depression

treated with nasal esketamine, whose clinical condition was evaluated using the Montgomery–Åsberg Depression Rating Scale (MADRS) and TATE. The main advantage of this paper relative to previous reports and studies is the assessment of disturbances in temporal experience[6].

Case description (Patient 1)

The patient, a male aged 35, first experienced psychological disturbances in his early 20s. Patient's ethnicity is Serbian. Initial symptoms included low mood, hopelessness, lack of motivation, and pronounced anxiety. He commenced psychiatric treatment at a university psychiatric clinic in 2012 with a diagnosis of a depressive disorder. Over the years, he experienced recurrent episodes of depressive symptoms, including persistent tension, anhedonia, social withdrawal, irritability, and intermittent suicidal ideation. He did not have any known family history of psychiatric disorders. His symptoms were treated with first-line antidepressants and regular outpatient follow-up. In between episodes, the patient was able to function despite the residual anhedonia. In his early 30s, the growing severity and functional impairment necessitated his first psychiatric hospitalization in April 2022. Although partial functional improvement occurred post-discharge, a relapse led to a second hospitalization in February 2024. Upon discharge, the patient continued to exhibit persistent depressive features–primarily loss of motivation, anhedonia, and a persistently low mood. Throughout this period, he underwent multiple trials of first-line antidepressants at adequate doses and durations, including sertraline (100 mg/day), duloxetine (120 mg/day), venlafaxine (225 mg/day), and fluoxetine (60 mg/day). Augmentations with atypical antipsychotics (e.g., olanzapine, quetiapine) yielded insufficient therapeutic gains. No substantial improvement confirmed TRD.

In light of irresponsiveness, nasal esketamine treatment was introduced. The regimen involved administration twice weekly (56 mg per session) for one month, followed by a reduction in frequency to once weekly (56 mg per session). Concurrent antidepressant therapy was: venlafaxine 225 mg/day. To monitor depressive symptoms and temporal disturbances, the MADRS and TATE scales were administered before each esketamine session. The patient was followed for ten weeks.

The MADRS total score–a measure of overall depressive symptom intensity–decreased from 39 at baseline to 19 by Week 5, representing a 51.2% reduction and indicating a therapeutic response, and reached 9 at Week 10, confirming clinical remission. Parallel to mood improvements, temporal disturbances also declined. TATE consists of 42 items, rated from 0 to 7 for frequency, intensity, and perceived impairment of atypical temporal experiences, with average values indicating overall severity. Items reflect phenomena such as a perceived slowing of time ("Sometimes I feel that time is slowing down without any immediate reason as if what we are doing will never end") or a reversal of temporal flow ("Sometimes I have the strange feeling that the direction of time is completely reversed, that time is going backwards"). At baseline, the patient's TATE score was 111.33. As treatment progressed and depressive symptoms improved, TATE scores gradually decreased, reaching a total of 24.67 by Week 10 (Figure 1), including a significant drop in prominent sets of disturbances concerning deceleration (5.58 to 0), planning (5.33 to 1.77) and a sense of being lost in time (2.5 to 0.6). Interestingly, the TATE total score dropped to the value of 66.00 in Week 4, which is close to the healthy control group's mean of sums score of 73.37[4], that is, one week before clinical remission as measured by MADRS.

Case Description (Patient 2)

The patient, a 27-year-old male, first experienced psychological disturbances in mid-adolescence (at age 17). Patient ethnicity is Serbian. Initial symptoms included low mood, hopelessness, lack of motivation, and a marked withdrawal from social interactions. He subsequently engaged in outpatient psychiatric treatment in his local area, yet the depressive symptoms–characterized by depressed mood, psychomotor slowing, and limited volition–persisted at a severe level. Despite multiple trials of first-line antidepressant therapies (clomipramine 150 mg/day, duloxetine 120 mg/day, venlafaxine 225 mg/day, mirtazapine 30 mg/day, sertraline 200 mg/day) and various augmentations with antipsychotics (risperidone 4 mg/day, cariprazine 1.5 mg/day, aripiprazole 10 mg/day, olanzapine 5 mg/day, clozapine 50 mg/day) as well as mood-stabilizing (lamotrigine 100 mg/day) and anxiolytic agents (pregabalin 225 mg/day), his functional status remained poor. He lived with his father, had been unemployed for an extended period, and continued to exhibit pervasive anhedonia and limited motivation. He did not have any known family history of psychiatric disorders.

By May–June 2024, due to the persistent and debilitating nature of his symptoms, he underwent inpatient treatment. Although there was a modest reduction in anxiety and irritability during hospitalization, he showed minimal overall improvement. Consequently, he was discharged with the same depressive features largely intact, including prominent social withdrawal and low drive. Given his poor response to multiple pharmacotherapies administered at adequate doses and durations, he met the criteria for TRD.

An intranasal esketamine regimen was introduced, initially at 56 mg per session twice weekly. Concurrent antidepressant therapy was: duloxetine 120 mg/day. At baseline, the patient’s MADRS score was 34, and the TATE total was 97.33, indicating marked temporal disturbances. By the beginning of the second week, MADRS decreased slightly to 31, although TATE remained elevated. In response to minimal clinical improvement, the esketamine dose was increased to 84 mg per session at the end of the second week. Thereafter, MADRS scores

declined steadily, reaching 12 at the start of Week 5, at which time TATE decreased to 70.33. By Week 6, the MADRS score was 5, and TATE had dropped to 55.66 as well (Figure 2), suggesting a near-complete resolution of both depressive symptoms and a significant reduction of temporal experience disturbances.

Discussion and Conclusions

These two cases illustrate the potential for nasal esketamine to alleviate not only core depressive symptoms but also less commonly assessed phenomenal aspects of lived experience, specifically regarding disturbed temporality. Both patients met the criteria for TRD after failing multiple trials of standard antidepressants and augmentation strategies. In each instance, esketamine administration was associated with reductions in MADRS scores, paralleled by improvements in the TATE.

Of particular interest, the first patient showed notable reductions in TATE one week prior to achieving the commonly accepted threshold for therapeutic response on MADRS. This may suggest that reductions in disturbances of time experience can, in some cases, precede more global reductions in depressive symptoms. Unfortunately, the second patient did not undergo sufficiently frequent TATE assessments to determine whether a similar temporal pattern occurred. We may speculate that early shifts in subjective temporal experience might serve as subtle leading indicators of later clinical remission – a hypothesis that future studies with closer interval measurements should clarify.

The close association between MADRS and TATE improvements in these cases supports the idea that restoring a more flexible or normalized sense of time may be an essential component of recovering from depressive states. Depression is often characterized by the subjective sensation of time standing still or slowing down, potentially exacerbating hopelessness and anhedonia[1,2]. Tools like TATE can aid in systematically capturing these

phenomenal changes without requiring extensive training in phenomenological interviewing[4,5]. Their use alongside standard symptom measures may thus yield a more comprehensive and subtle picture of patient recovery.

Temporal experience in depression has been systematically examined through multiple methodological frameworks, demonstrating the comprehensive scope of research in this domain. Phenomenological investigations constitute the primary methodological approach, wherein researchers examine the lived temporal experience through detailed analysis of first-person accounts. Complementing this qualitative foundation, experimental psychological studies have employed quantitative methodologies to assess temporal perception under controlled conditions. Narrative research methodologies represent a third distinct approach, analyzing personal discourse patterns and temporal narratives of patients. Furthermore, several investigations have adopted methodological pluralism, integrating phenomenological and psychological approaches to provide multidimensional perspectives on temporal disturbances in mood disorders. This methodological diversity underscores the robust empirical foundation underlying the current understanding of temporal dysfunction in depressive conditions[7,8].

However, this work has several limitations. As a two-patient case series, these findings cannot establish causality, and no long-term follow-up was conducted to determine whether these improvements in time perception and depressive symptoms persisted. Additionally, it remains unclear whether the improvements in TATE scores actively contribute to remission or simply reflect broader symptom relief. Larger-scale studies using frequent time-point assessments are warranted to investigate these dynamics more thoroughly and to validate TATE as a sensitive phenomenological marker of early treatment response.

In conclusion, these cases suggest that nasal esketamine may benefit both core depressive symptoms and the subjective perception of time–a dimension of experience seldom

tracked in standard clinical practice. Observations of TATE improvements preceding MADRS response underscore the potential utility of phenomenological measures in capturing subtle, early changes. By systematically integrating instruments like TATE into treatment monitoring, clinicians may gain insights into how rapid-acting antidepressants affect the deeper layers of a patient's lived experience.

- Assessing temporal experiences is essential in depression and oftentimes missed in routine depression assessment.
- Lived temporal disturbance improvement might precede improvement in standard-measured depression symptoms.

Declarations

Ethics approval and consent to participate: Patients gave written informed consent to participate in the assessments described. All information has been de-identified to protect anonymity.

Consent for publication: Written informed consent for publication was obtained from the patients.

Availability of data and materials: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Stefan Jerotić and Milica Nestorović evaluated the patients through TATE. Marcin Moskalewicz and Anastazja Szuła developed and validated TATE. Stefan Jerotić and Janko Nešić took the lead in writing the manuscript, and Marcin Moskalewicz reviewed and edited it. All authors approved the final form.

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Keywords: esketamine, treatment-resistant depression, phenomenology, Transdiagnostic Assessment of Temporal Experience (TATE)

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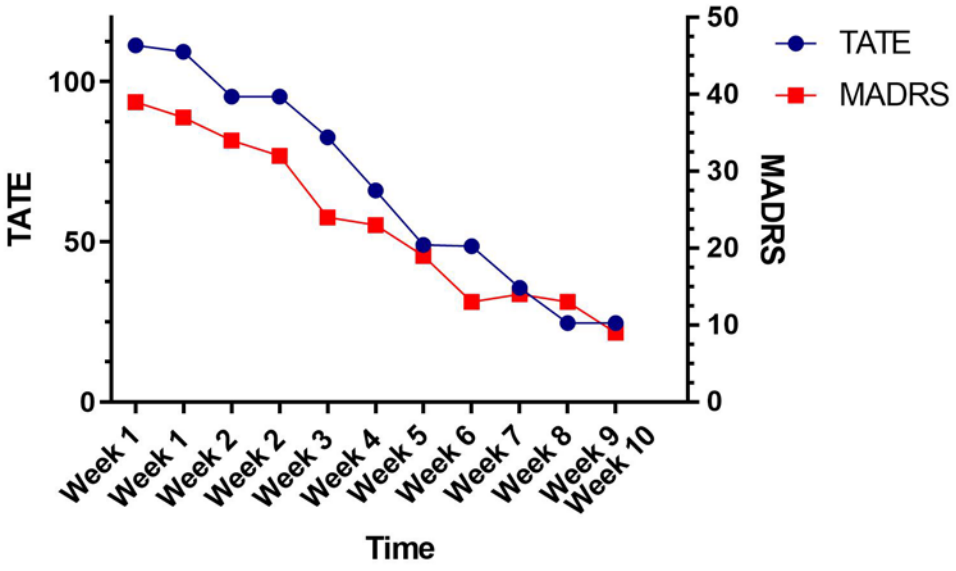

Figure 1. TATE and MADRS scores over 10 weeks of treatment with esketamine in a 35-year-old patient (N=1)

Note: Changes in *Transdiagnostic Assessment of Temporal Experience* (TATE) and *Montgomery–Åsberg Depression Rating Scale* (MADRS) scores over the course of nasal esketamine treatment. TATE scores (blue line, left Y-axis) decreased from 111.33 at baseline to 24.67 by Week 10, while MADRS scores (red line, right Y-axis) showed a parallel reduction from 39 at baseline to 9 at Week 10.

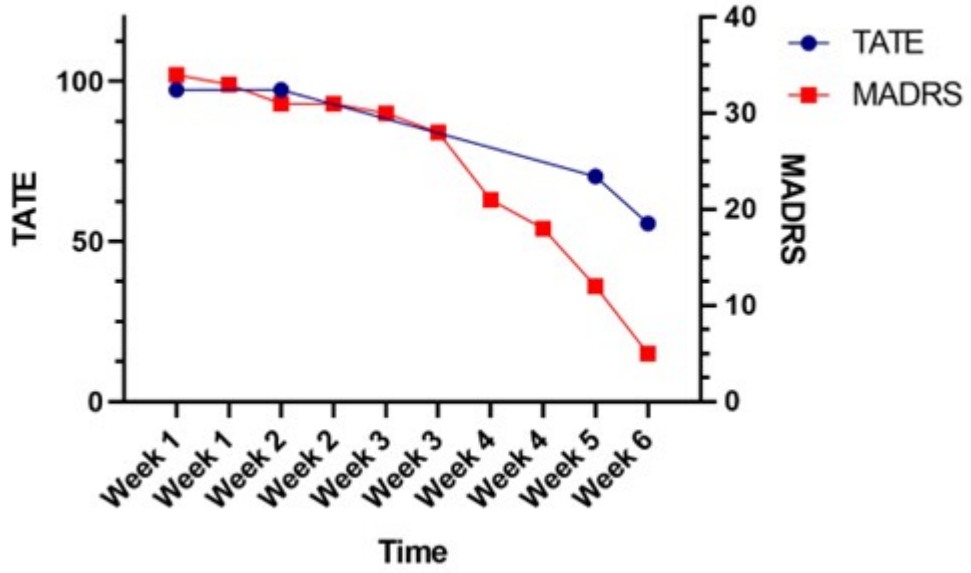

Figure 2. TATE and MADRS scores over 6 weeks of treatment with esketamine in a 27-year-old patient (N=1)

Note: Changes in *Transdiagnostic Assessment of Temporal Experience* (TATE) and *Montgomery–Åsberg Depression Rating Scale* (MADRS) scores over the course of nasal esketamine treatment. At the second Week 2 point, the dose of esketamine was raised to 84 mg. TATE was measured only in Week 1, Week 2, Week 5 and Week 6. TATE scores (blue line, left Y-axis) decreased from 97.33 at baseline to 55.66 at Week 6, while MADRS scores (red line, right Y-axis) showed a reduction from 34 at baseline to 5 at Week 6.