Long term adverse effects of oral esketamine in patients with major depressive disorder

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Abstract

Treatment-resistant depression (TRD) remains a major clinical challenge due to the limited efficacy and side effect burden of traditional antidepressants. Esketamine, a fast-acting NMDA receptor antagonist, has emerged as a promising alternative; however, its long-term side effects, particularly in oral form, are not well understood. This study aimed to investigate the frequency and severity of adverse effects associated with oral esketamine over an eleven-week period in patients with TRD. In study, 75 participants received oral esketamine twice weekly, with doses titrated between 0.5 and 3.0 mg/kg. Adverse effects were systematically assessed before each treatment session using the Ketamine Side Effect Tool (KSET). Results showed that the overall burden of side effects remained stable over time. No significant changes were observed in the severity or frequency of individual side effects, including dissociation, drowsiness, and memory or concentration difficulties. These findings suggest that oral esketamine is well tolerated over the short term, even at higher doses, without evidence of cumulative toxicity. Further research with larger samples and extended follow-up periods is necessary to fully assess the long-term safety and therapeutic potential of oral esketamine for TRD.

Introduction

Depression is one of the most prevalent and disabling mental health disorders worldwide, affecting over 300 million people and posing significant personal, societal, and economic burdens (WHO, 2023). The number of people living with depression has risen substantially over the past three decades, with marked disparities across gender, age, and regions (Liu et al., 2024). Despite the widespread impact of this disorder, access to effective treatment remains limited. Only 7–28% of individuals with depression receive care, and even among those treated, long-term remission is often not achieved (Chisholm et al., 2016; Eder et al., 2023).

Current first-line treatments, including antidepressant medication and psychotherapy, have notable limitations. Antidepressants typically take several weeks to produce therapeutic effects and are associated with a range of side effects—such as emotional blunting, sexual dysfunction, and weight gain—that can reduce adherence (Eder et al., 2023). Psychotherapy, though effective, is often inaccessible due to long waitlists and a shortage of

qualified professionals. Additionally, many patients experience recurrent symptoms or fail to respond altogether, leading to treatment-resistant depression (TRD), a condition characterized by insufficient response to multiple classes of antidepressants.

In recent years, ketamine has emerged as a promising alternative treatment for TRD, offering rapid antidepressant effects—sometimes within hours—by modulating glutamatergic neurotransmission and enhancing synaptic plasticity (Sattar et al., 2018; Ragone et al., 2023). Esketamine, the S-enantiomer of ketamine, has a higher affinity for NMDA receptors and is approved as a nasal spray for TRD treatment. However, both intravenous and intranasal administration require clinical supervision and are associated with high costs, limiting their scalability and accessibility (Kumar et al., 2024).

Oral esketamine is gaining attention as a practical alternative. It enables self-administration in outpatient settings, reduces healthcare costs, and offers a more stable pharmacokinetic profile that may lower the risk of acute side effects (Can et al., 2021; Dutton et al., 2023). A recent study reported that oral esketamine showed comparable efficacy to intravenous administration while yielding lower dropout rates, suggesting better tolerability (Kumar et al., 2024). Despite these advantages, systematic data on the long-term safety of oral esketamine are still lacking, especially regarding potential adverse effects.

Esketamine's known side effects include dissociation, dizziness, sedation, and cognitive issues such as memory or attention difficulties (Yang et al., 2021). These effects raise concerns about tolerability, particularly during long-term use or at higher doses. Although studies have assessed safety profiles for intravenous and intranasal routes, the oral route remains underexplored. Moreover, chronic ketamine use—especially in recreational contexts—has been linked to cognitive impairment, bladder dysfunction, and other long-term risks (Zhang & Ho, 2016; Breeksema et al., 2022).

To address this gap, the Ketamine Side Effect Tool (KSET) was developed to systematically track ketamine-related adverse effects in clinical settings, covering acute and long-term symptoms across multiple domains (Short et al., 2020). While KSET has been applied in studies of intranasal and intravenous ketamine, its use in oral esketamine studies is still limited. As oral esketamine becomes more widely considered for TRD, it is essential to evaluate its safety profile comprehensively, especially regarding cumulative or progressive side effects.

This study aims to assess the frequency and severity of adverse effects during oral esketamine treatment over an 11-week period in patients with TRD, using the KSET. Specifically, it investigates whether certain side effects intensify over time. These insights are critical for determining the long-term tolerability and clinical feasibility of oral esketamine as a sustained treatment option for TRD.

Methods

Study Design

This study examined data from the open-label extension phase (Phase 3) of a larger multicenter clinical trial investigating the effects of oral esketamine in patients with major

depressive disorder (Smith-Apeldoorn et al., 2024). The trial was conducted at three psychiatric institutes in the Netherlands: the University Center Psychiatry in Groningen, the Pro Persona Depression Expertise Center in Nijmegen, and the Parnassia Psychiatric Institute in Den Haag. Phase 3 was conducted between February 2021 and November 2024.

Participants

Eligible participants in this study were aged 18 to 80 years, had a current major depressive episode diagnosed according to DSM-5 criteria, and exhibited at least moderately severe depressive symptoms (Hamilton Depression Rating Scale score >18). They were required to be on stable doses of established antidepressant medication and meet the study's definition of treatment-resistant depression (TRD), defined as an insufficient lifetime response to at least three different classes of antidepressant medications. Participants with a lifetime history of psychotic disorders, bipolar disorder, moderate to severe substance-use disorder, or active suicidal intent were excluded. Written informed consent was obtained from all participants.

In total, 76 participants were included in the analysis, from which the Ketamine Side Effect Tool (KSET) assessments were collected. Data from participants who did not complete the full six-week off-label treatment period were excluded from the primary analysis.

Intervention

Participants received oral esketamine twice per week over a six-week period. The dosing regimen was flexible, ranging from 0.5 mg/kg to 3.0 mg/kg, as determined by clinical judgment based on individual tolerability and response. Unlike the earlier phases of the study, adherence was not formally monitored in Phase 3. The treatment was administered by the participants themselves in an outpatient setting, allowing participants to take the medication at home. This dosing strategy was chosen to assess the feasibility and safety of individualized esketamine titration.

Outcome Measures

The primary outcome measure was the frequency and severity of adverse effects assessed using the Ketamine Side Effect Tool (KSET) (Short et al., 2020). KSET assessments were conducted prior to each treatment session (before oral esketamine administration) during the eleven-week treatment period, ensuring consistent pre-treatment documentation of adverse effects.

Statistical Analysis

75 participants were analyzed at week 1, 51 participants were analyzed at week 6 and 45 participants were analyzed at week 11. The differences in numbers of participants analyzed at each timepoint is due to missing data. A linear mixed-effects model was used to evaluate changes across time. All statistical analyses were conducted using RStudio (version 4.2.2, RStudio Team, 2023). To investigate changes in adverse effects and clinical outcomes over time, linear mixed-effects models (LMMs) were employed. This approach accounts for the unbalanced structure of the data, including missing data points and varying numbers of assessments per participant across the observation period. The primary analysis focused on changes in individual KSET item scores between Week 1 (baseline) and Week 6, as well as Week 11 of oral esketamine treatment. LMMs were run separately for each KSET item, with timepoint as a fixed effect and participant ID as a random intercept to model repeated measures. Covariates such as age and gender were included in the models to account for

their potential influence on side effects and depressive symptoms. These covariates were chosen based on previous literature suggesting that they may affect treatment outcomes, although no significant differences in results were found after correction for these variables.

Additionally, to further investigate patterns of adverse effects over time, we analyzed whether participants reported a score of 1 or higher on any of the KSET items across the three time points. This analysis aimed to identify if certain side effects were reported more frequently at any stage of treatment. A similar approach was applied to scores higher than 3, to examine whether participants reported more severe problems with specific side effects as the treatment progressed.

Changes in total KSET scores were evaluated using similar LMMs to determine whether side effects, depressive symptoms, and cognitive performance changed significantly over time. In addition, exploratory visualizations and LMMs were used to assess broader trends in side effect severity across all available timepoints, to determine whether certain adverse effects persisted, resolved, or fluctuated over time. False discovery rate (FDR) correction was applied to adjust for multiple comparisons.

Regarding missing data, we assumed that missing data were missing at random (MAR), as this is consistent with the patterns of missingness observed in the dataset. Sensitivity analyses were conducted to explore the robustness of our findings under different assumptions of the missing data mechanism (e.g., missing completely at random (MCAR) and missing not at random (MNAR)).

Results

A total of 75 participants with major depressive disorder (MDD) were included in the analysis. The majority of the participants were using an antidepressant treatment and all participants were receiving oral esketamine treatment 2x per week at the time of the study (Table 1).

Table 1
Demographic and clinical characteristics (n = 75).

Variable	***Value***
Gender, n (%)	*Female (65,3%), Male (34,7%)*
Age, mean (SD)	*43.4 (8.5)*
Duration of current depression in years, mean (SD)	*13.8 (9.4)*
Number of depressive episodes, mean (SD)	*3.9 (2.8)*
Age at first depression, mean (SD)	*23.5 (12.6)*

Antidepressant use (%)	*73%*

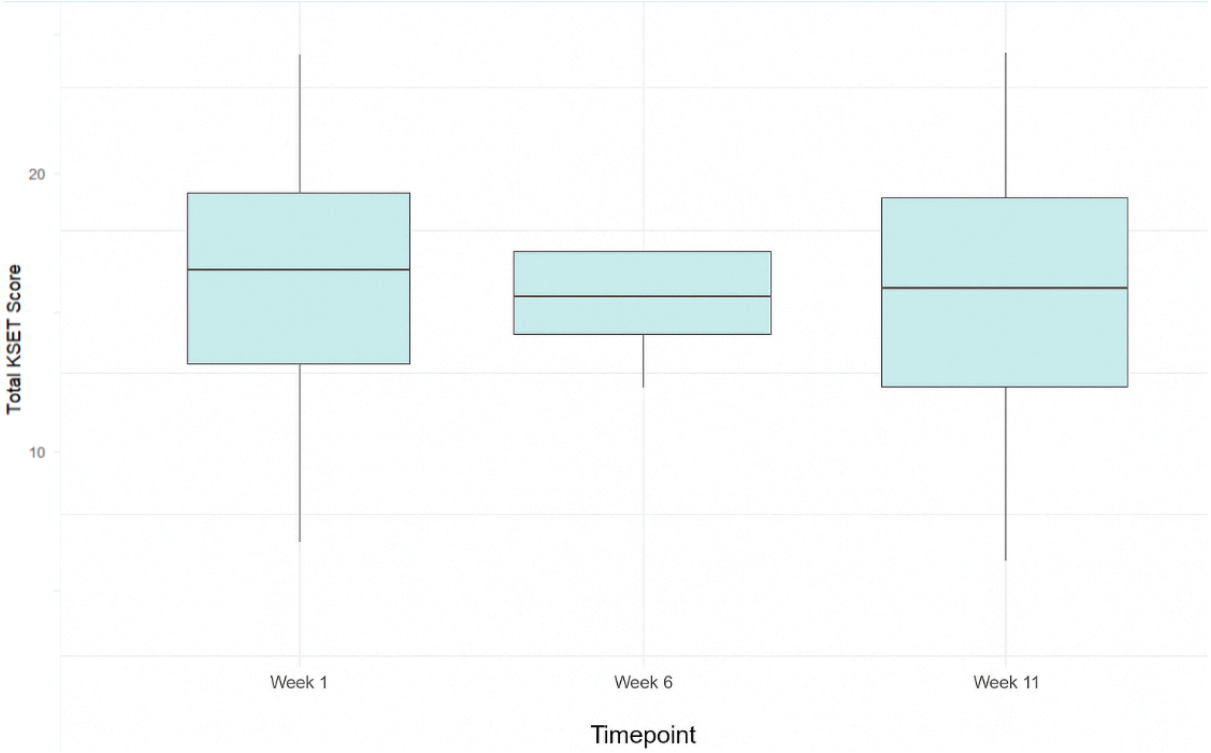

Figure 1. Total KSET scores in patients with major depressive disorder over time. The total side effect burden, as measured by the KSET, was assessed at Week 1 (baseline), Week 6, and Week 11 of oral esketamine treatment.

Total KSET scores, representing the overall burden of side effects, remained stable throughout the treatment period. As shown in figure 1, there were no significant changes in total KSET scores between Week 1 (baseline), Week 6, and Week 11. Linear mixed-effects modeling confirmed the absence of a time-related effect on total side effect burden. The analysis revealed no significant differences in total KSET scores between the three timepoints, suggesting that overall side effect severity remained stable throughout treatment ($p > .05$).

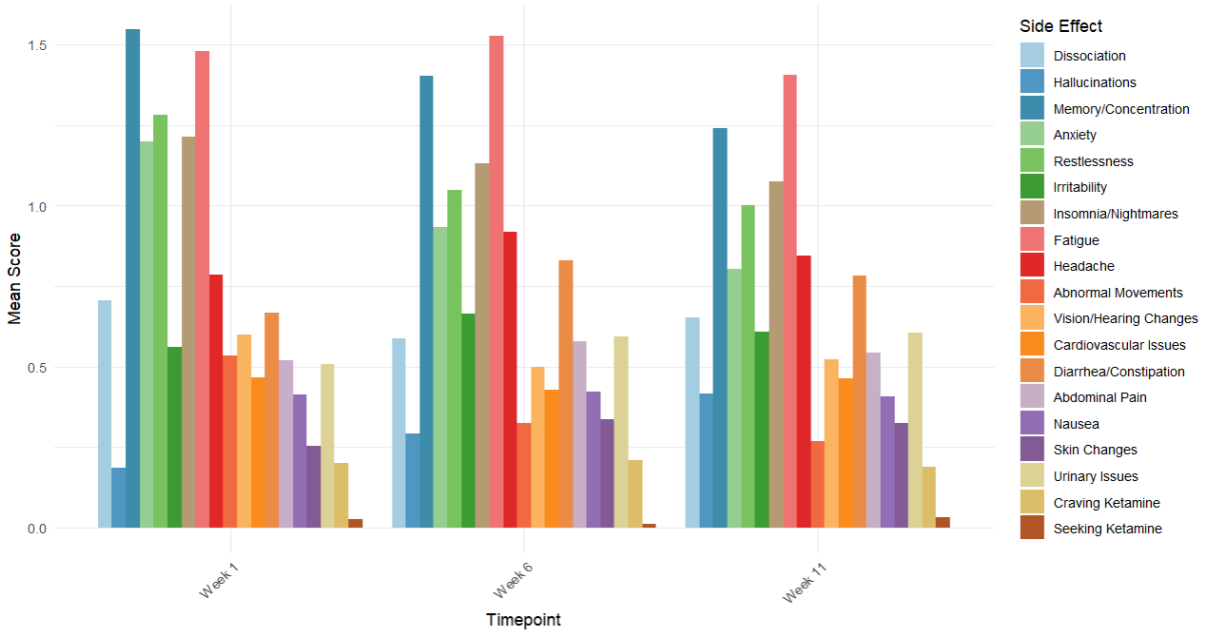

Figure 2. Mean scores of individual side effects reported on the KSET in patients undergoing oral esketamine treatment for major depressive disorder. Timepoints represent Week 1 (baseline, before treatment), Week 6, and Week 11 of treatment. Linear mixed-effects models were conducted for each KSET item separately.

Mean scores for each of the 19 individual KSET items were analyzed across the three timepoints. As visualized in Figure 2, the most frequently reported side effects included memory/concentration difficulties, drowsiness, and insomnia/nightmares. However, linear mixed-effects models indicated no statistically significant changes over time for any individual side effect items (all $p > .05$).

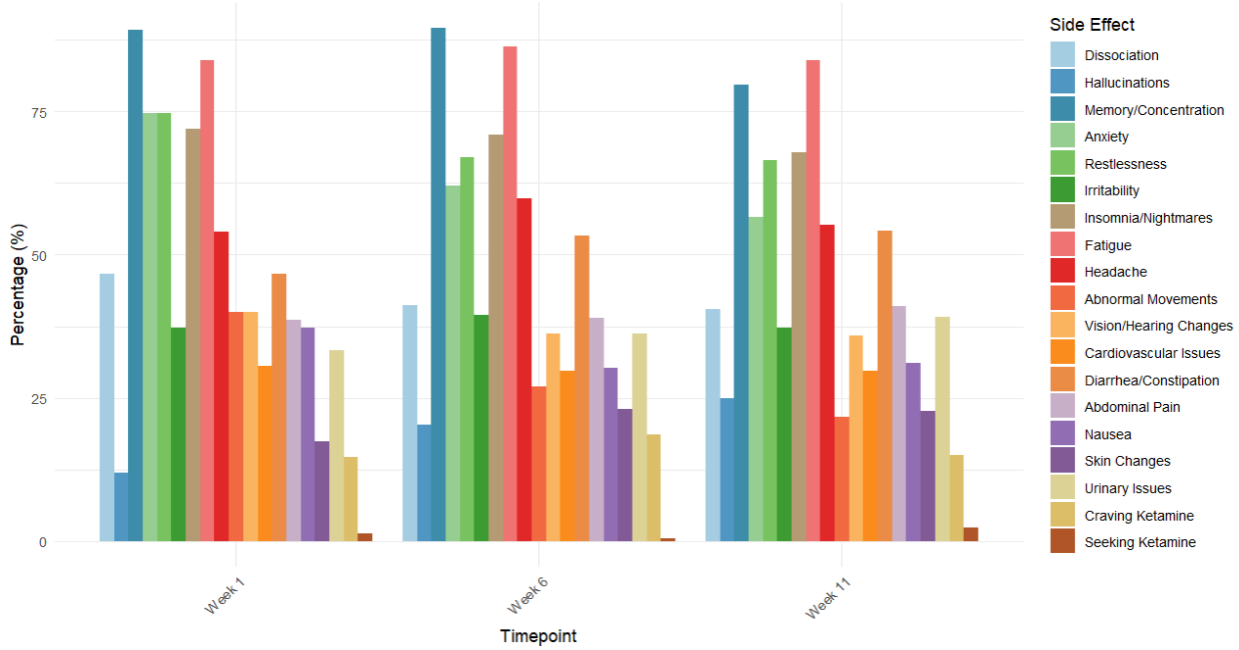

Figure 3. Number of participants reporting each KSET side effect (score ≥ 1) during oral esketamine treatment for major depressive disorder. Timepoints represent Week 1 (baseline), Week 6, and Week 11 of treatment.

The number of participants reporting a score ≥ 1 for each KSET item was calculated for Week 1, Week 6, and Week 11. As shown in Figure 3, the frequency of reported side effects remained relatively stable across time. Linear mixed-effects models conducted per side effect did not reveal any significant differences in reporting rates across timepoints (all p > .05).

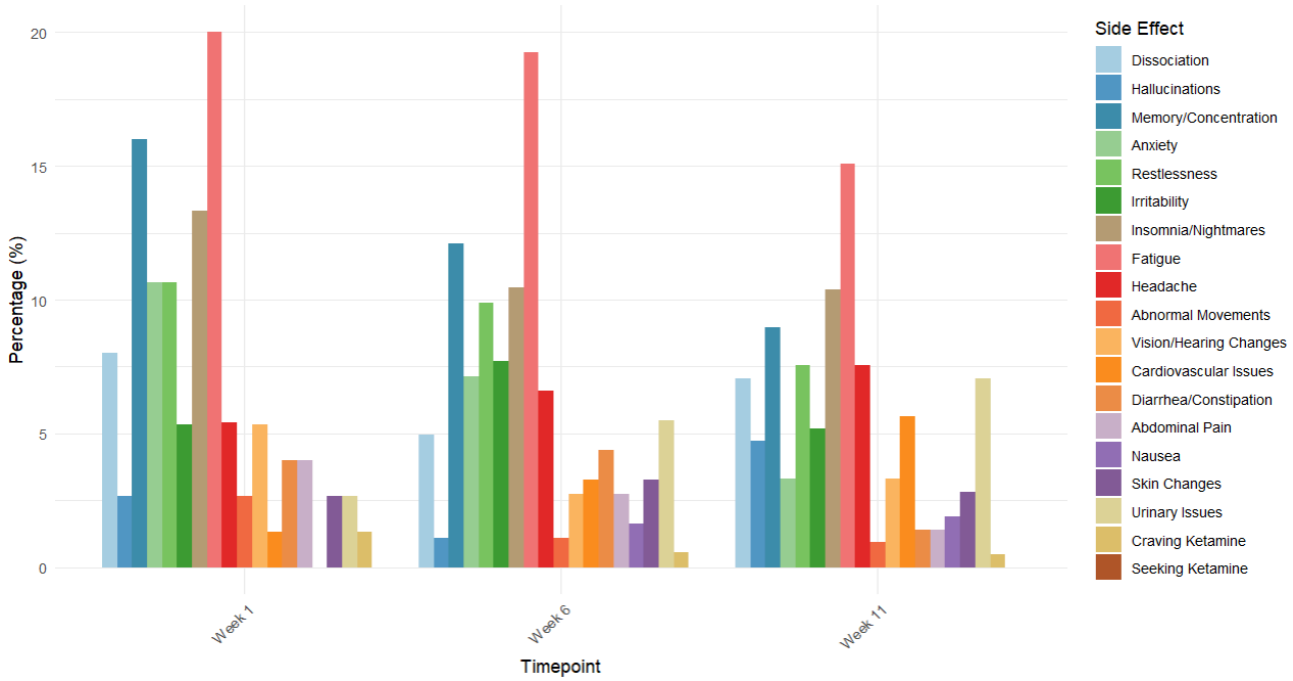

Figure 4. Number of participants reporting each KSET side effect (score ≥ 3) during oral esketamine treatment for major depressive disorder. Timepoints represent Week 1 (baseline), Week 6, and Week 11 of treatment. Linear mixed-effects models conducted per side effect did not reveal any significant

The number of participants reporting a score ≥ 3 for each KSET item was calculated for Week 1, Week 6, and Week 11. As shown in Figure 4, the frequency of reported side effects remained relatively stable across time aswell. No significant differences were found in the proportion of participants reporting each side effect over the treatment period (all p > .05).

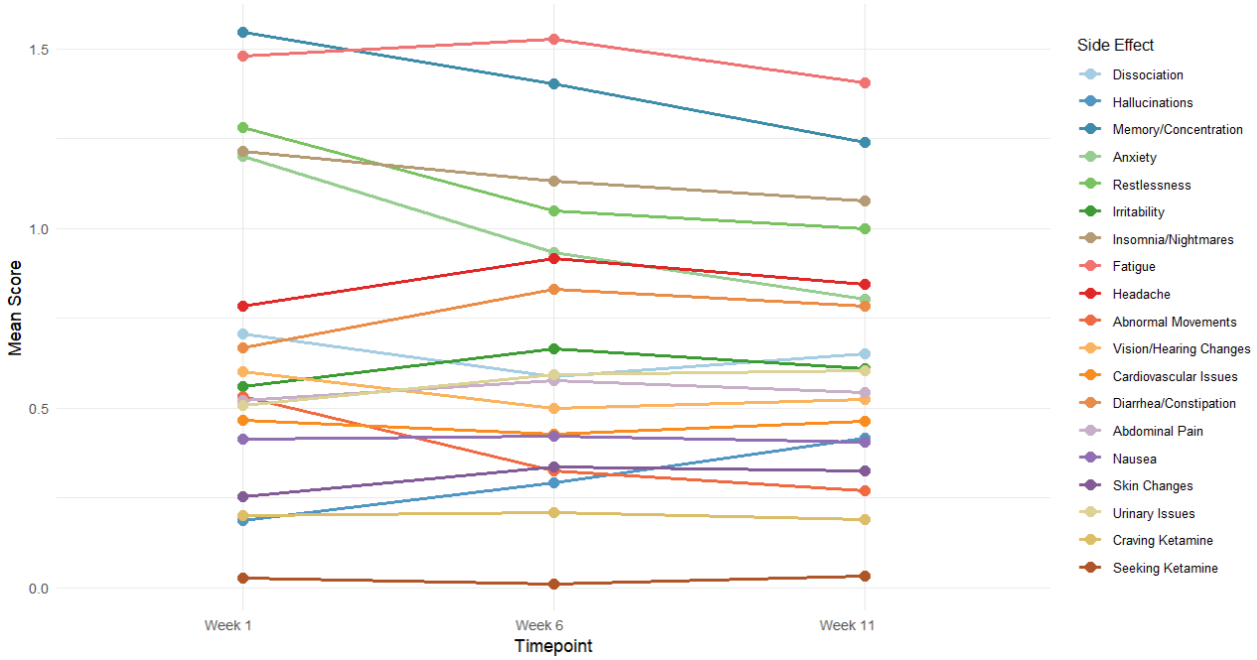

Figure 5: Changes in mean KSET side effect scores over time during oral esketamine treatment in patients with major depressive disorder. Side effect severity was tracked across Week 1 (baseline), Week 6, and Week 11.

Figure 5 displays mean trajectories for each item over the three timepoints. No clear time-related increases or decreases were observed, and linear mixed-effects models showed no significant longitudinal changes in side effect scores. Linear mixed-effects models per side effect indicated that none of the items showed significant changes over time (all $p > .05$)

Discussion

This study examined the long-term side effect profile of oral esketamine in individuals with treatment-resistant depression (TRD) over an 11-week period, using the Ketamine Side Effect Tool (KSET). Overall, the findings suggest that oral esketamine is well-tolerated, with no significant increase in the total burden of side effects or in individual adverse effects across the treatment duration.

KSET assessments, conducted prior to each dose, revealed that dissociative symptoms, drowsiness, concentration/memory difficulties, and insomnia were among the most commonly reported adverse effects. Importantly, these did not worsen over time, either in frequency or severity. This pattern aligns with previous studies suggesting that many ketamine-related side effects are acute and transient, rather than progressive when administered in a structured clinical context (Bayes et al., 2024).

The stability of side effects over time may be partly explained by the pharmacokinetic advantages of oral administration. Compared to intravenous or intranasal routes, oral esketamine produces more gradual plasma concentration peaks, which may reduce the likelihood of severe acute side effects (Can et al., 2021; Dutton et al., 2023). Additionally, participants in this study received titrated doses based on individual tolerability, which likely enhanced safety and minimized escalation of adverse effects.

A key concern in the literature on chronic ketamine use is cognitive impairment, including difficulties with attention, memory, and executive functioning (Zhang & Ho, 2016). In this study, cognitive-related side effects such as memory and concentration issues were frequently reported but did not show significant change over time. This may reflect the relatively controlled dosing and structured setting in which treatment occurred, which contrasts sharply with patterns of recreational ketamine use where cognitive decline is more commonly observed.

However, it is also possible that the KSET was not sensitive enough to detect subtle cognitive changes. While useful for capturing patient-reported symptoms across a wide range of domains, the KSET lacks detailed neuropsychological testing. Future research should incorporate more rigorous cognitive assessments to evaluate the potential impact of esketamine on domains such as attention, verbal memory, and executive function.

The study's open-label design, absence of a placebo or comparator group, and limited follow-up duration are important limitations. Without a control group, it is difficult to determine whether reported side effects were attributable to esketamine itself, the underlying depressive disorder, or concomitant medications. Symptoms like fatigue, sleep disturbance, and concentration problems are also common in major depressive disorder, which complicates interpretation. Randomized controlled trials (RCTs) with appropriate controls are needed to isolate the specific contribution of oral esketamine to side effect profiles.

Another limitation is missing data across timepoints, which may have introduced bias. Although linear mixed-effects models are robust to missingness, the decreasing number of participants over time reduces statistical power and may obscure small but meaningful trends. Moreover, rare or delayed-onset side effects may not be captured within the 11-week observation window.

Although the study did not focus on treatment efficacy, evaluating side effects in isolation limits conclusions about the overall risk-benefit balance. Future studies should examine how the tolerability of oral esketamine relates to its antidepressant effects. If stable side effects are accompanied by meaningful clinical improvements, this could support oral esketamine as a viable long-term strategy for managing TRD.

A major strength of this study is the use of the KSET, a structured and validated tool tailored specifically for ketamine side effect monitoring. This allowed for consistent and comprehensive tracking across multiple domains. However, supplementing self-report tools with objective clinical measures such as cognitive testing, laboratory monitoring, or neuroimaging would strengthen future research and provide a fuller picture of esketamine’s safety.

In summary, this study contributes valuable evidence to the growing literature on oral esketamine by showing that its side effect profile remains stable over an extended treatment period. These findings are promising, but must be interpreted in light of methodological limitations. Larger, controlled studies with longer follow-up and multidimensional safety assessments are essential to fully determine the long-term feasibility of oral esketamine in clinical practice.

Conclusion

In conclusion, this study provides encouraging evidence that oral esketamine, administered over a period of up to eleven weeks, is well tolerated in patients with treatment-resistant depression (TRD). Across multiple timepoints, side effects remained largely stable, with no significant increase in severity or frequency, even with continued use. Notably, symptoms commonly associated with ketamine, such as dissociation, cognitive impairment, or physical discomfort, did not show progressive worsening. These findings suggest that oral esketamine, when carefully monitored, may represent a safe and feasible longer-term treatment strategy for TRD. While future controlled trials with larger samples and longer follow-up are needed, these results support the ongoing development and implementation of oral esketamine as a practical antidepressant option.

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