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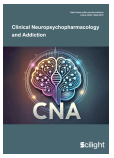

Article

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Sex- and Age-Stratified Differences in Antidepressant Response to Intranasal Esketamine in Treatment-Resistant Depression: A Secondary Analysis of the REAL-ESK Study

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Abstract: Background: Intranasal esketamine (ESK-NS) is an effective treatment for treatment-resistant depression (TRD), but whether antidepressant outcomes differ by sex and age remains insufficiently explored. Methods: This secondary analysis of the REAL-ESK study included 210 patients with TRD treated with ESK-NS in routine clinical practice and assessed at baseline (T0), one month (T1), and three months (T2). The primary outcome was change in Montgomery–Åsberg Depression Rating Scale (MADRS) scores. Repeated-measures ANOVA tested Time and Time × Sex effects, with post-hoc contrasts corrected using the Holm procedure. Response and remission at T2 were compared by sex. Exploratory analyses stratified patients by age (<65 vs. ≥65 years). Results: MADRS scores decreased markedly over time (Time: $F = 340.707$, $p < 0.005$), with a significant Time × Sex interaction ($F = 3.283$, $p = 0.043$). At T2, men had lower MADRS scores than women ($\Delta = -3.95$, Holm $p = 0.023$) and showed higher response and remission rates. In age-stratified analyses, sex differences were small and non-significant among participants <65 years. In those ≥65 years, the T2 contrast numerically favored men, but did not reach significance in post-hoc Holm's correction and should be considered exploratory. Safety outcomes and discontinuation rates were broadly comparable between sexes. Conclusions: ESK-NS was associated with substantial antidepressant improvement in a real-world TRD cohort. Findings suggest a modest overall male advantage, while age-stratified

patterns remain exploratory. Endocrine, vascular, inflammatory, pharmacokinetic, and treatment-context factors should be investigated in prospective studies.

Keywords: esketamine; intranasal; treatment-resistant depression; sex differences; aging; MADRS; real-world evidence

1. Introduction

Treatment-resistant depression (TRD) is a major driver of disability, premature mortality, and healthcare costs, with a substantial proportion of patients failing to respond adequately to sequential monoaminergic antidepressants despite guideline-concordant care [1–3]. Intranasal esketamine (ESK-NS), a non-competitive NMDA receptor antagonist, introduces a rapidly acting, plasticity-based mechanism that is neurobiologically distinct from conventional agents [4,5]. Converging preclinical and translational evidence points to glutamatergic disinhibition, enhanced AMPA throughput, activity-dependent BDNF–TrkB signaling, and downstream mTOR-mediated synaptogenesis as key processes through which ketamine/esketamine alleviates depressive symptoms [4,6–9]. Notably, these cascades are sensitive to endocrine context and to age-related shifts in neural and immune function—dimensions that remain underexplored in routine clinical practice even though they plausibly influence treatment trajectories [10].

Sex differences in major depressive disorder (MDD) are well described: women exhibit higher lifetime prevalence and, in many samples, greater chronicity [11–16]. Across the lifespan, estradiol and progesterone-derived neurosteroids modulate cortical excitability and synaptic remodeling through rapid, nongenomic signaling at membrane-associated receptors and through regulation of glutamate/GABA balance [17]; they also engage BDNF-dependent pathways that support dendritic spine dynamics and long-term potentiation, involving circuits related to emotional regulation [18–20]. In this context, neuroactive steroids such as pregnanolone and zuralonone have also shown promising effect in treating depressive disorders [21].

In contrast, post-menopausal hypoestrogenism is associated with attenuated plasticity signaling and altered stress responsivity [22–24], while in men androgenic pathways may confer partially distinct trophic and immunomodulatory effects relevant to synaptogenesis [25,26]. Because ESK-NS harnesses activity-dependent plasticity [27], hormonal milieus that augment—or dampen—these mechanisms could shape clinical outcomes across sex and age. Additional age-linked factors—including neuroinflammatory tone, vascular and white-matter integrity, and pharmacokinetic/pharmacodynamic variation—may further gate the efficiency with which drug-evoked plasticity translates into durable symptom change [28–30].

Despite these biologically plausible modifiers, most clinical evaluations of ESK-NS have emphasized average effects, even in real-world populations [31–38], but limited attention was given to heterogeneity by sex and age [39]. Observational cohorts are uniquely positioned to address this gap by capturing effectiveness under routine conditions, characterizing tolerance and adherence, and quantifying subgroup trajectories beyond the constraints of narrowly selected trial samples [40].

Against this mechanistic and clinical backdrop, in this secondary analysis of the REAL-ESK study [31] we leveraged real-world data to quantify the overall antidepressant effects of ESK-NS across three months, to test for sex differences in longitudinal MADRS trajectories and categorical outcomes (response and remission), and to examine effect modification by age using a clinically relevant cut-off (<65 vs. ≥65 years).

2. Materials and Methods

2.1. Study Design and Cohort

This is a secondary analysis of REAL-ESK [31], a multicenter, observational, retrospective Italian cohort evaluating the effectiveness and safety of ESK-NS in routine TRD care, with assessments at T0 (baseline), T1 (~1 month), and T2 (~3 months). The original REAL-ESK reports describe eligibility (adults with TRD in MDD) [32], concomitant SSRI/SNRI as per regulatory guidance, and routine clinical exclusions; data were abstracted from medical records across university, hospital, and community sites.

Primary outcome for this analysis was MADRS total score at T0/T1/T2. Response was defined as ≥50% MADRS reduction from baseline [32]; remission as MADRS ≤ 10 at T2 [32]. Safety outcomes included treatment-emergent adverse events (TEAEs) [41]. The study was approved by the local ethics committee of the Università degli Studi di Brescia (Protocol Number: NP5331).

ESK-NS dosing aligns with the specifications detailed in the summary of product characteristic: Age < 65 years: Induction phase (Weeks 1–4): Initial dose for day 1: 56 mg, subsequent doses: 56 mg or 84 mg twice a week. Maintenance phase (Weeks 5–8): 56 mg or 84 mg once a week. From Week 9: 56 mg or 84 mg every 2 weeks or once a week.

Age > 65 years: Induction phase (Weeks 1–4): Initial dose for day 1: 28 mg, subsequent doses: 28 mg, 56 mg or 84 mg twice a week; all dose adjustments must be made in 28 mg increments. Maintenance phase (Weeks 5–8): 28 mg, 56 mg or 84 mg once a week; all dose adjustments must be made in 28 mg increments. From Week 9: 28 mg, 56 mg or 84 mg every 2 weeks or once a week; all dose adjustments must be made in 28 mg increments.

2.2. Statistical Analysis

Analyses were conducted in SPSS 20.0 and JASP 0.16.4 (two-sided, $\alpha = 0.05$). Continuous variables are mean ± SD; categorical n (%). Longitudinal change in MADRS was evaluated via repeated-measures ANOVA (rm-ANOVA) with Time (T0, T1, T2) as within-subject factor. When sphericity was violated (Mauchly's test), significance was estimated applying the Greenhouse–Geisser correction. Post-hoc comparisons for the sex factor at individual time points used Holm correction to control type-I error. Effect sizes were reported as partial eta squared (η^2p) for rm-ANOVA and Cohen's d for between-sex contrasts and within-group standardized change from baseline (Hedges' *g* considered where appropriate). Response and remission were compared between sexes with χ^2 tests, and risk ratios with 95% CIs were computed when relevant. We further performed an age-stratified analysis (<65 vs. ≥65 years): within each stratum, rm-ANOVA on Time was run separately by sex (with sphericity checks/Greenhouse–Geisser), and male–female differences in change (T0→T1, T0→T2) were tested using Welch's *t*. Holm correction was applied separately within each age stratum across the two post-hoc contrasts (T0→T1 and T0→T2), and both uncorrected and Holm-adjusted p-values are reported. Means ± SD for Time × Sex and effect sizes for all repeated-measures models were reported consistently as partial eta squared (η^2p). As a sensitivity analysis, we additionally tested the main longitudinal sex effect using a covariate-adjusted model including age, baseline MADRS severity, and the presence of psychiatric comorbidity as covariates. Fully adjusted models within the ≥65 age stratum were not performed because of the limited subgroup size and the consequent risk of model overfitting.

All patient data were treated confidentially and anonymously, and the study was conducted in line with the Helsinki Declaration [42].

3. Results

3.1. Sample Characteristics

The present secondary analysis included 210 adults with unipolar TRD (mean age 52.84 ± 12.63 years). The sample comprised 107 males (51.0%) and 103 females (49.0%). As shown in Table 1, baseline features were consistent with a real-world TRD population treated in tertiary and community-based psychiatric settings. Psychiatric comorbidities and sociodemographic indices are reported in Table 1.

Table 1. Socio-demographic and clinical characteristics at baseline (N = 210).

Variable	Value
Age (years), mean ± SD	**52.84 ± 12.63**
Gender	Males **107** (51%) Females **103** (49%)
Previous treatment failures (n = 210), mean ± SD	**3.20 ± 1.99**
Marital status	Not married **69** (33.1%) Married/cohabiting **117** (55.5%) Widowed **24** (11.4%)
Occupation	Unemployed **89** (42.7%) Employed **113** (53.7%) Other **8** (3.6%)
Children	0 children **96** (45.9%) 1 child **112** (53.4%) 2 children **2** (0.7%)
Psychiatric comorbidities	Psychosis **2** (1.1%) Anxiety **14**(6.8%) OCD **12** (5.7%) Eating Disorders **5** (2.5%) PTSD **4** (2.1%) SUD **13** (6.4%) Personality disorders **28** (13.5%)
MADRS total score, overall, mean ± SD	34.77 ± 9.79
MADRS total score, males, mean ± SD	35.35 ± 9.45
MADRS total score, females, mean ± SD	34.17 ± 10.14
MADRS total score, <65 years, mean ± SD	34.80 ± 10.01
MADRS total score, ≥65 years, mean ± SD	34.63 ± 8.84

3.2. ESK-NS Antidepressant Effect and Gender Differences

In the overall sample (N = 210), baseline MADRS scores were comparable by sex (T0: females 34.17 ± 10.14; males 35.35 ± 9.45). rm-ANOVA showed a strong Time effect (Type III SS; F = 340.707, df_GG = 1.810, MS = 15132.726, $p < 0.001$, $\eta^2p = 0.297$), with Mauchly's test indicating sphericity violation (W = 0.895, $\chi^2 = 22.445$, $p < 0.001$; εGG = 0.905). The Time × Sex interaction was significant (F = 3.283, $p = 0.043$, $\eta^2p = 0.003$), as was the main Sex effect (F = 4.643, $p = 0.032$, $\eta^2p = 0.012$) (Figure 1).

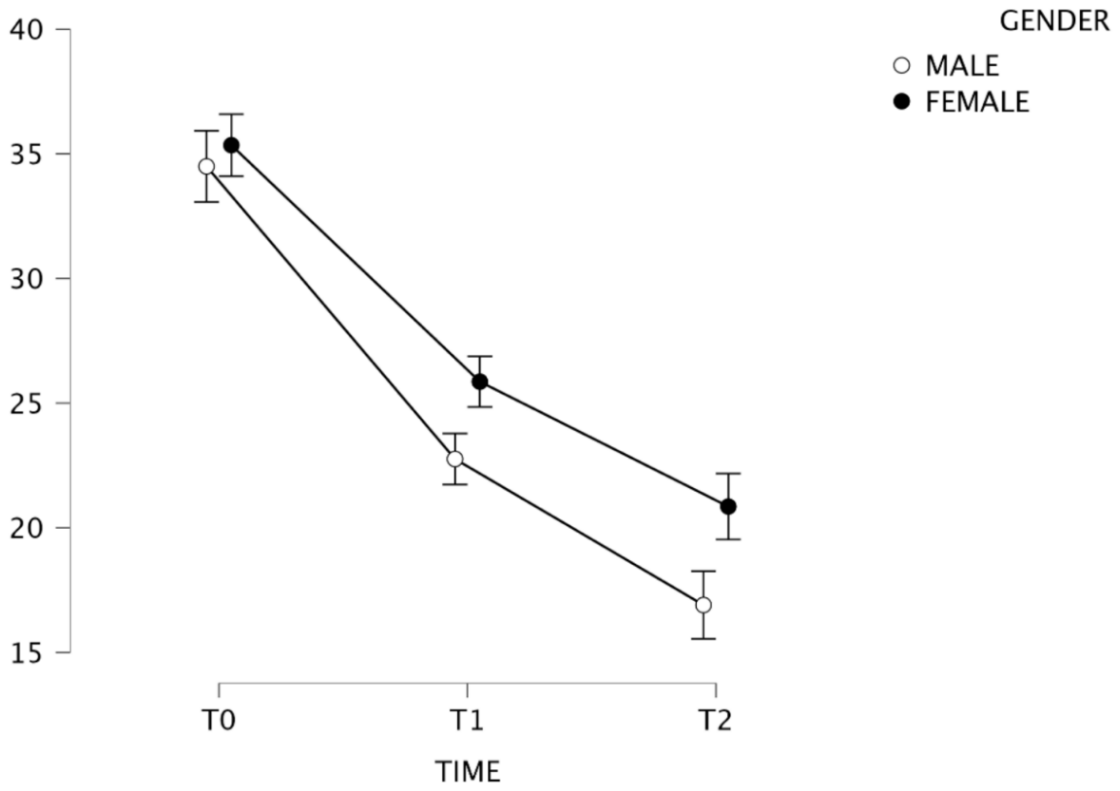

Figure 1. Mean MADRS and standard errors bars at baseline (T0), one month (T1), and three months (T2) after ESK-NS initiation, stratified by sex.

Descriptively, MADRS declined for both sexes at T1 (females 25.86 ± 9.90; males 22.76 ± 10.60) and further at T2 (females 20.85 ± 10.64; males 16.90 ± 10.59). Post-hoc, the between-sex contrast at T2 favored males (Δ = −3.951, SE = 1.420, $t = -2.783$, d = 0.388, Holm $p = 0.023$), while T1 was smaller and not significant (Δ = −3.102, SE = 1.420, $t = -2.185$, d = 0.305, Holm $p = 0.089$). Within-sex standardized changes versus baseline were large: in males, T0→T2 $d = 1.728$ and T0→T1 $d = 1.153$; in females, T0→T2 $d = 1.340$ and T0→T1 $d = 0.932$ (all Holm $p < 0.001$). In the covariate-adjusted sensitivity analysis including age, baseline MADRS severity, and psychiatric comorbidity, the direction of the longitudinal sex-related pattern remained unchanged, supporting the robustness of the primary analysis.

3.3. Response and Remission at T2

In the overall sample (N = 210), categorical outcomes mirrored the continuous results. Response was 59.2% in males (63/107) vs. 41.1% in females (42/103), $\chi^2 = 6.879$, $p = 0.009$. Remission was 32.0% (34/107) vs. 16.8% (17/103), $\chi^2 = 6.608$, $p = 0.010$ (Figure 2).

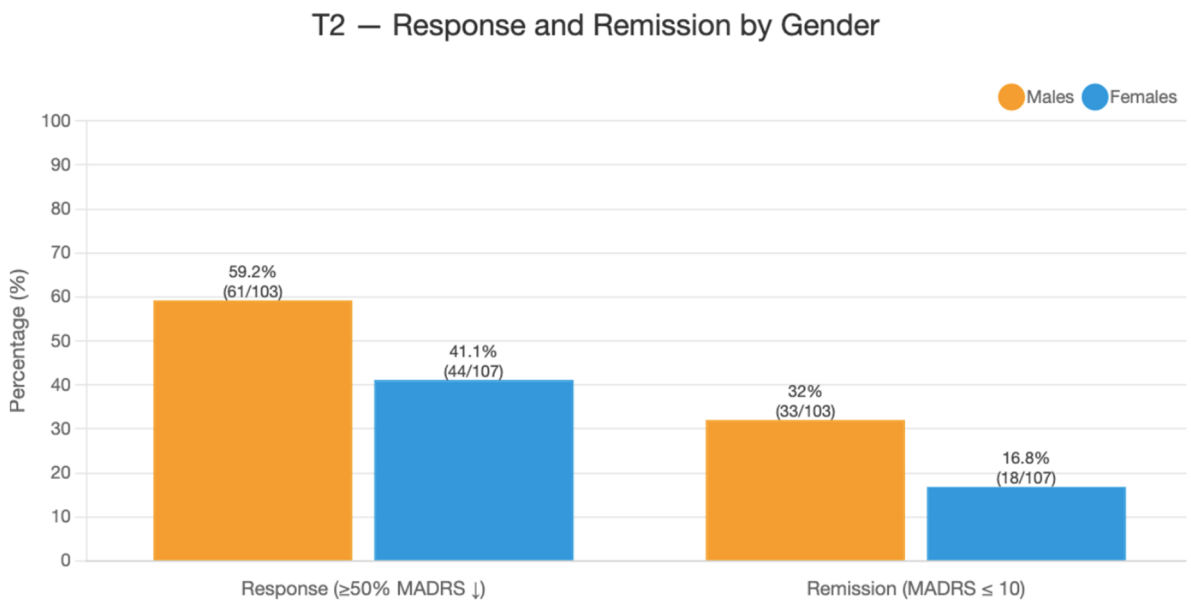

Figure 2. Response (≥50% MADRS reduction) and remission (MADRS ≤10) at T2 by sex; bars display percentages with counts (n/N).

3.4. Age-Stratified Analysis (<65 vs. ≥65 Years)

To probe potential effect modification, we stratified the sex × time ESK-NS antidepressant effect by age (<65 vs. ≥65 years). This analysis was conducted in participants with complete MADRS data across T0, T1, and T2. In participants aged <65 years, the Time effect was marked within each sex (males N = 82: $F(2,162) = 150.43$, $p < 0.001$, $\eta^2p = 0.650$; females N = 86: $F(2,170) = 120.80$, $p < 0.001$, $\eta^2p = 0.587$). However, male–female differences in MADRS reduction were small and non-significant: +1.78 points at T1 (uncorrected $p = 0.169$; Holm-adjusted $p = 0.304$) and +2.33 points at T2 (uncorrected $p = 0.152$; Holm-adjusted $p = 0.304$).

In participants aged ≥65 years, Time also remained significant within each sex (males N = 22: $F(2,42) = 26.73$, $p < 0.001$, $\eta^2p = 0.572$; females N = 20: $F(2,38) = 41.80$, $p < 0.001$, $\eta^2p = 0.723$). Male–female differences in MADRS reduction were numerically larger, favoring males: +4.32 points at T1 (uncorrected $p = 0.098$; Holm-adjusted $p = 0.102$) and +6.53 points at T2 (uncorrected $p = 0.051$; Holm-adjusted $p = 0.102$). However, these contrasts did not reach statistical significance after correction. Accordingly, the ≥65 findings should be interpreted cautiously as exploratory and hypothesis-generating, particularly given the smaller subgroup sizes in the older age stratum (Figure 3).

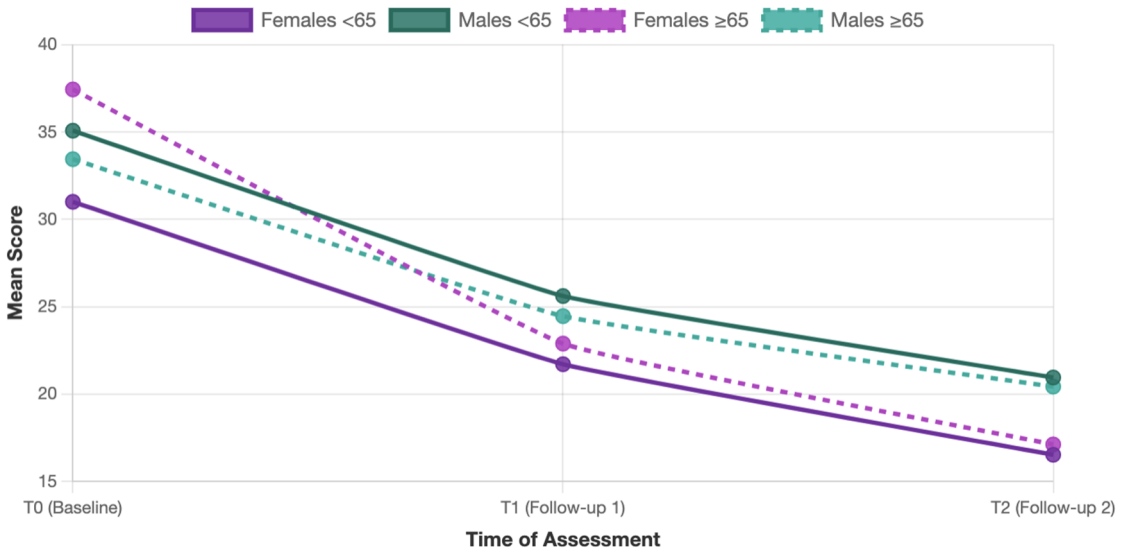

Figure 3. Mean MADRS (±SE) at T0/T1/T2 by sex and age stratum (<65 vs. ≥65 years).

3.5. Safety and Discontinuation

TEAEs were balanced by sex with no significant differences for hypertension (χ^2 = 2.217, p = 0.330), dissociative phenomena (χ^2 = 2.488, p = 0.647), sedation (χ^2 = 1.506, p = 0.471), hypomania (χ^2 = 0.119, p = 0.942), psychomotor agitation (χ^2 = 0.176, p = 0.916), anxiety (χ^2 = 0.069, p = 0.966), headache/dizziness (χ^2 = 2.312, p = 0.510), and paresthesia/diplopia (χ^2 = 0.069, p = 0.966) (Table 2). Discontinuation occurred in 10/107 males (9.3%) and 4/103 females (3.9%), with no statistically significant between-sex difference (χ^2 = 2.517, p = 0.113).

Table 2. Adverse events during ESK-NS by sex (N = 210; % within sex).

Adverse Event	Males (N = 107) N (%)	Females (N = 103) N (%)	P (χ^2)
Hypertension	10 (9.7%)	5 (5.1%)	0.206
Dissociative phenomena	45 (41.7%)	38 (37.2%)	0.444
Sedation	21 (19.4%)	26 (25.5%)	0.329
Hypomania	3 (2.8%)	2 (2.2%)	0.682
Psychomotor agitation	2 (2.1%)	2 (1.5%)	0.969
Anxiety	4 (4.2%)	4 (3.7%)	0.956
Headache/dizziness	10 (9.0%)	13 (13.1%)	0.447
Paresthesia/diplopia	4 (4.2%)	4 (3.7%)	0.956

4. Discussion

In this naturalistic real-world cohort, intranasal esketamine was associated with a marked and sustained reduction in depressive symptoms over three months. Both women and men benefited substantially; however, by T2 men showed lower average MADRS scores and higher rates of response and remission. This difference was small among participants younger than 65 years, whereas a numerically larger male–female separation was observed in the ≥65 subgroup. However, this age-stratified pattern did not survive correction for multiple comparisons and should therefore be regarded as exploratory rather than as evidence of a definitive sex-by-age effect. Because adverse events and discontinuation were comparable between sexes, tolerability is unlikely to account for these patterns. A coherent interpretation situates these findings within current models of rapid-acting antidepressants. Ketamine and esketamine are thought to act by releasing glutamatergic constraints, enhancing AMPA throughput, and triggering activity-dependent BDNF and mTOR signaling that promotes synaptogenesis in corticolimbic circuits [43–45]. These plasticity mechanisms do not operate in isolation: they are shaped by a complex interplay of biological factors that shift across the lifespan. While endocrine changes are often cited as estradiol facilitates dendritic spine formation and potentiates BDNF/TrkB signaling [18–20], the observed sex-by-age pattern likely reflects the convergence of multiple mechanisms. Although post-menopausal estradiol decline could represent one biologically plausible contributor to altered drug-evoked plasticity, this possibility remains speculative in the absence of direct endocrine or menopausal-status data. The observed pattern should therefore be interpreted within a broader multifactorial framework that also includes vascular aging, immune-inflammatory tone, white-matter integrity, pharmacokinetic/pharmacodynamic variability, and concomitant medications.

For instance, sex-related differences in vascular aging, immune-inflammatory tone, and white-matter integrity could equally determine how efficiently synaptic remodeling translates into clinical improvement. Furthermore, differences in androgenic signaling or the cumulative impact of chronic neuroinflammation may contribute to the divergent trajectories observed in older cohorts.

This biologically grounded account does not exclude other contributors. Modest differences in exposure, arising from age- or sex-related variation in absorption, distribution, metabolism, or clearance, could shift the dose response curve. Crucially, the differential use of co-medications that dampen cortical excitability, such as benzodiazepines, merits equal consideration, as these agents may blunt plasticity signals and may be prescribed more frequently in specific subgroups [46,47]. Heterogeneity in illness course, comorbidities, or cognitive reserve could also condition response [48–51]. Our modeling strategy emphasized within-subject change and applied sphericity-aware repeated-measures analyses, and categorical outcomes converged with continuous measures, but an observational design cannot fully eliminate residual confounding. A clinically relevant corollary is the possibility of menstrual cycle modulation [52]. Phases characterized by higher estradiol or more favorable estradiol to progesterone ratios could theoretically enhance the same synaptogenic cascades that esketamine engages. Although cycle phase, menopausal status, and hormone therapy were not captured here, the age stratified pattern observed warrants prospective studies. Such research should test not only the impact of hormonal fluctuations, but also how they interact with vascular and metabolic health to influence the speed, magnitude, or durability of benefit. From a practical standpoint, the message is twofold. First, esketamine appears broadly effective in TRD

across sexes, with large within-group effects that are clinically meaningful. Second, average trajectories may vary by sex and age, but the present age-stratified findings should be interpreted cautiously and require confirmation in larger samples specifically powered to test sex-by-age interactions. This should inform expectation-setting and follow-up without discouraging treatment in women, many of whom also respond or remit. In routine care, these exploratory findings may support careful monitoring of treatment trajectories across sex and age groups, without implying that sex or menopausal status should currently guide treatment selection. Future studies should clarify whether endocrine status, vascular health, inflammatory burden, pharmacokinetic exposure, and sedative co-medication meaningfully influence ESK-NS outcomes.

Strenghts and Limitations

The study's strengths include its multicenter, real-world context, the convergence between continuous and categorical outcomes, and transparent longitudinal modeling with appropriate corrections for sphericity and multiple comparisons. Key limitations are intrinsic to observational data: the absence of randomization, incomplete control over concomitant treatments, and the lack of endocrine or pharmacokinetic phenotyping. Although a covariate-adjusted sensitivity analysis supported the direction of the main sex-related finding, fully adjusted models within the ≥65 subgroup were not performed because the limited sample size would have increased the risk of overfitting and unstable estimates. Accordingly, the age-stratified findings should be interpreted as exploratory and require replication in larger samples specifically powered to test sex-by-age interactions while adjusting for relevant clinical covariates.

5. Conclusions and Future Perspectives

Future trials assessing menstrual-cycle phase or endocrine-informed strategies in post-menopausal populations could test whether hormonal context moderates drug-evoked plasticity and clinical response. Parallel biomarker programs, linking clinical change to EEG indices of synaptic readiness, serum BDNF, inflammatory signatures, and imaging of synaptic density or connectivity, could clarify mechanisms and sharpen prediction. Finally, exposure–response studies with pharmacokinetic sampling and careful mapping of co-medications would determine how dosing, metabolism, and treatment context interact with sex and age to shape outcomes. If confirmed, these insights would help translate a generally effective intervention into a more precisely targeted therapy for TRD.

Author Contributions

Conceptualization: G.d., L.P., C.C., and M.P. (Mauro Pettorruso); methodology: G.d., L.P., C.C., and M.P. (Mauro Pettorruso); formal analysis: G.d. and L.P.; investigation: C.C., S.P., A.S., A.D.T., M.D., A.R., A.I., G.T., C.D.P., V.S., D.D.B., V.M., M.P. (Milena Piccirillo), F.R., T.V., A.B., M.L., L.M., and A.D.C.; data curation: G.d., L.P., C.C., and M.P. (Mauro Pettorruso); writing—original draft preparation: G.d., L.P., C.C., and M.P. (Mauro Pettorruso); writing—review and editing: all authors; supervision: M.P. (Mauro Pettorruso). 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 Institutional Review Board (or Ethics Committee) of Università degli Studi di Brescia (Protocol Number: NP5331).

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 not publicly available due to ethical and privacy restrictions protecting participant confidentiality. Anonymized data may be made available from the corresponding author

upon reasonable request, subject to ethics approval and institutional regulations, and will be retained for at least 10 years after publication.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT to support language editing and improve the clarity and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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