No conflict of interest

https://doi.org/10.1016/j.nsa.2025.105779

PS01-0248

NEUROSCIENCE APPLIED 5 (2026) 105778

ESKETAMINE AS A MODULATOR OF EMOTIONAL BLUNTING IN TREATMENT-RESISTANT DEPRESSION: CLINICAL INSIGHTS FROM A NATURALISTIC STUDY

S.E. Rossi [1], R. Guglielmo [1,2], A. Zizzi [1], M. Marino [1], E. Briasco [1], E. Cavanna [1], F. Schiavon [1], A. Mazzocchi [2], G. Giacomini [2], G. Serafini [1,2]

[1] *University of Genoa, Department of Neuroscience Rehabilitation- Ophthalmology-Genetics- Maternal and Child Health- Section of Psychiatry, Genoa, Italy;* [2] *IRCCS Ospedale Policlinico San Martino- Genoa- Italy, Psychiatry, Genoa, Italy*

Introduction: Antidepressants are widely used to alleviate depressive symptoms, but they may also lead to adverse emotional effects, notably emotional blunting a condition marked by emotional detachment, low motivation, and reduced affective responsiveness. Selective serotonin reuptake inhibitors (SSRIs) are frequently associated with this phenomenon [1]. Evidence suggests that serotonergic antidepressants can impair emotional awareness by increasing subjective difficulty in identifying feelings [2], while multimodal agents such as vortioxetine have been linked to reductions in emotional blunting [3]. Supporting this, d'Andrea et al. [4] observed greater improvement in emotional blunting among patients with treatment-resistant depression treated with vortioxetine combined with intranasal esketamine (ESK-NS), compared to those receiving SSRI/SNRI plus ESK-NS. Despite its clinical relevance, the psychological, neurobiological, and pharmacological mechanisms underlying emotional blunting remain poorly understood. Notably, no prior studies have specifically investigated the effect of esketamine nasal spray on emotional awareness using validated psychometric tools.

Aims: This study aimed to investigate changes in subjective emotional awareness following esketamine nasal spray treatment in patients with treatment-resistant depression (TRD). We also examined whether concomitant treatment with SSRIs, compared to other antidepressant classes, influenced emotional awareness outcomes.

Methods: Eighteen TRD outpatients (7 male, 11 female, age 56,1 ± 9,7) were recruited from the San Martino Hospital outpatient unit. Emotional awareness was assessed using the Difficulty Identifying Feelings (DIF) subscale of the Toronto Alexithymia Scale (TAS-20), a validated measure of alexithymia comprising three subscales: DIF, Difficulty Describing Feelings (DDF), and Externally Oriented Thinking (EOT). DIF scores were recorded at baseline and after three months of treatment with intranasal esketamine. Participants were stratified based on their concurrent antidepressant treatment: nine received SSRIs and nine received other antidepressant classes. The Wilcoxon signed-rank test was used to assess within-group changes in DIF scores from baseline to post-treatment. Between-group differences (SSRI vs. non-SSRI) in baseline characteristics and treatment outcomes were evaluated using the Mann–Whitney U test. In addition, a bivariate correlation analysis was conducted to explore the association between DIF scores and depression severity as measured by the Hamilton Depression Rating Scale.

Results: After three months of esketamine treatment, a significant improvement in emotional awareness, as measured by a reduction in DIF scores, was observed across the full sample ($p = 0.046$). No significant differences in DIF scores were found between the SSRI and non-SSRI groups at either time point. Additionally, there was no significant correlation between DIF scores and depression severity, as measured by the Hamilton Depression Rating Scale.

Conclusions: These findings suggest that esketamine treatment may enhance emotional awareness in patients with TRD, potentially mitigating emotional blunting regardless of the concurrent antidepressant medication class. The lack of difference between SSRI and non-SSRI groups supports the hypothesis that esketamine may counteract serotonergic-induced emotional dampening. This underscores the therapeutic value of esketamine not only in reducing depressive symptoms but also in improving affective functioning in TRD patients.

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No conflict of interest

https://doi.org/10.1016/j.nsa.2025.105778

PS01-0249

NEUROSCIENCE APPLIED 5 (2026) 105779

EFFICACY AND SAFETY OF PSILOCYBIN IN TREATMENT-RESISTANT MAJOR DEPRESSION (EPISODE): RESULTS OF A RANDOMIZED ACTIVE PLACEBO-CONTROLLED TRIAL

L.J. Mertens [1], M. Koslowski [2], F. Betzler [2], M. Brand [1], R. Evens [2], L. Krätner [1], A. Jungaberle [3], H. Jungaberle [3], T. Majić [2], C.N. Schmitz [1], A. Ströhle [2], D. Scharf [1], M. Spangemacher [1], M. Wolff [3], Z. Assadi [2], B. Scharif [2], L. Becher [2], L.V. Färber [1], N. Kirchen [1], E. Kulakova [2], L. Kunz [1], A. Meijer [2], B. Rohrmoser [1], S. Wellek [4], M. Berger [4], G. Gründer [1]

[1] *Central Institute of Mental Health, Department of Molecular Neuroimaging, Mannheim, Germany;* [2] *Charité Universitätsmedizin Berlin - Campus Charité Mitte, Department of Psychiatry and Psychotherapy, Berlin, Germany;* [3] *MIND, Foundation, Berlin, Germany;* [4] *Central Institute of Mental Health, Department of Biostatistics, Mannheim, Germany*

Background: Psilocybin shows promise in treating depression, although methodological limitations warrant further research. This study investigated the efficacy and safety of high-dose oral psilocybin (25 mg) with adjunct psychotherapy in 144 adults with treatment-resistant depression (TRD).

Methods: This is a bicentric, double-blind, phase 2b, active placebo-controlled trial. Patients were recruited predominantly from out-patient settings at two university hospitals in Germany. Male or female patients with TRD of moderate to severe degree, aged 25-65, without any somatic or psychiatric contraindication and withdrawn from antidepressant medication were eligible. They were randomized to two doses six weeks apart: placebo (100 mg nicotinamide) followed by 25 mg psilocybin, 5 mg psilocybin followed by 25 mg psilocybin, or 25 mg psilocybin followed by either 5 mg or 25 mg psilocybin, embedded in seven psychotherapeutic sessions. Primary endpoint was treatment response (≥50% reduction on the Hamilton Rating Scale for Depression [HAMD17]) six weeks after the first dose. Secondary endpoints included response at Week 1 and 12, and HAMD17 change from baseline at Weeks 1, 6 and 12. An intention-to-treat strategy was used for the main efficacy analyses, all randomized participants were included in the safety analysis set. The trial is registered at ClinicalTrials.gov, NCT03429075. The study design has been published previously in Mertens et al. [1].

Results: Between June, 10th 2021 and December, 5th 2023, 144 patients (59 females [41%], 85 males [59%]) were enrolled and randomized into the trial, balanced across groups. 47 participants in the 25-mg-, 48 participants in the 5-mg- and 47 participants in the nicotinamide-group were included in the primary efficacy analysis at Week 6. Mean baseline HAMD17 scores ranged from 21.46 to 22.40 across groups. Response rates at Week 6 did not differ significantly between groups (25 mg: 17%, 5 mg: 13%, nicotinamide: 11%). At Week 1, the 25-mg-group showed higher response rates (34%) compared to the nicotinamide- (6%) and 5-mg- (10%) groups (Odds Ratio 25 mg vs. nicotinamide: 7.60; 95% CI: 2.29, 34.75). A linear mixed model predicting HAMD17 scores showed significant effects for 25mg vs. nicotinamide at Week 6 (β=-4.60; 95% CI: -7.01, -2.18; adjusted p=0.0004), with a strong effect also at Week 1 (β=-4.89, 95% CI: -7.31, -2.48). At Week 12, after all participants had received at least one high-dose psilocybin, there were no significant group differences, but strong estimated average changes from baseline across groups. High-dose psilocybin was linked to adverse events, predominantly acutely. Dynamic changes in suicidal ideation or behavior occurred in all groups.

Conclusion: Although the primary endpoint of categorical treatment response after six weeks was not met, 25 mg psilocybin with adjunct psychotherapy was