

Real-world experience of esketamine use to manage treatment-resistant depression: A multicentric study on safety and efficacy (REAL-ESK study)

Giovanni Martinotti^{1,2}, Antonio Vita^{3,4}, Andrea Fagiolini⁵, Giuseppe Maina⁶, Alessandro Bertolino⁷, Bernardo Dell’Osso⁸, Alberto Siracusano⁹, Massimo Clerici¹⁰, Antonello Bellomo¹¹, Gabriele Sani^{12,13}, Giacomo d’Andrea^{1*}, Roberto Delle Chiaie¹⁴, Andreas Conca¹⁵, Stefano Barlati^{3,4}, Giorgio Di Lorenzo⁹, Pasquale De Fazio¹⁶, Sergio De Filippis¹⁷, Giuseppe Nicolò¹⁸, Gianluca Rosso⁶, Alessandro Valchera¹⁹, Domenica Nucifora²⁰, Stefania Di Mauro²⁰, Roberta Bassetti²¹, Vassilis Martiadis²², Miriam Olivola²³, Sandro Belletti²⁴, Ileana Andriola⁷, Marco Di Nicola^{12,13}, Mauro Pettoruso¹, Roger S. McIntyre^{25,26,27,28,29}, Massimo di Giannantonio¹ and the REAL-ESK Study Group³⁰

¹ Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D’Annunzio, Chieti, Italy

² Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield AL10 9AB, UK

³ Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

⁴ Department of Mental Health and Addiction Services, ASST Spedali Civili of Brescia, Italy

⁵ School of Medicine, Department of Molecular Medicine, University of Siena, Siena, Italy

⁶ Department of Neurosciences "Rita Levi Montalcini", University of Torino, Turin, Italy

⁷ Università degli Studi di Bari "Aldo Moro", Italy

⁸ Department of Biomedical and Clinical Sciences Luigi Sacco and Aldo Ravelli Center for Neurotechnology and Brain Therapeutic, University of Milan, Milano, Italy

⁹ Chair of Psychiatry, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

¹⁰ Dipartimento di Medicina e Chirurgia, Università degli studi Milano Bicocca, Dipartimento di Salute Mentale e Dipendenze ASST Monza, Italy

¹¹ Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy

¹² Department of Neuroscience, Section of Psychiatry, Università Cattolica del Sacro Cuore, Rome, Italy

¹³ Department of Psychiatry, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

- ¹⁴ Department of Neuroscience and Mental Health-Policlinico Umberto I Hospital, Sapienza University of Rome, 00161 Rome, Italy
- ¹⁵ Psychiatric Service of the Health District of Bozen, Bozen-Bolzano, Italy
- ¹⁶ Psychiatry Unit, Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy
- ¹⁷ Neuropsychiatric Clinic, Villa Von Siebenthal, Genzano di Roma, Italy
- ¹⁸ Department of Mental Health and Addiction, ASL Roma5, Rome, Italy
- ¹⁹ Villa S. Giuseppe Hospital, Hermanas Hospitalarias, Ascoli Piceno, Italy
- ²⁰ MDSMA Taormina-Messina Sud ASP di Messina, Italy
- ²¹ SPDC Frosinone - ASL Frosinone, Italy
- ²¹ Department of Mental Health and Addiction Services, Niguarda Hospital, Milan, Italy
- ²² ASL Napoli 1 Centro, Department of Mental Health, Napoli, Italy
- ²³ Department of Brain and Behavioural Science, University of Pavia, Italy
- ²⁴ Mental Health Department, Azienda Unità Sanitaria Locale (AUSL) Umbria 2, Italy
- ²⁵ Mood Disorders Psychopharmacology Unit, Poul Hansen Family Centre for Depression, University Health Network, Toronto, ON, Canada
- ²⁶ Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada
- ²⁷ Canadian Rapid Treatment Center of Excellence, Mississauga, ON, Canada
- ²⁸ Brain and Cognition Discovery Foundation, Toronto, ON, Canada
- ²⁹ Department of Psychiatry, University of Toronto, Toronto, ON, Canada
- ³⁰ **REAL-ESK Study Group: Cinzia Niolu** (University of Rome Tor Vergata, Italy), **Chiara di Natale** (Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, Chieti, Italy), **Francesco di Carlo** (Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, Chieti, Italy), **Rebecca Colavecchio** (Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, Chieti, Italy), **Rosalba Carullo** (Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, Chieti, Italy), **Arianna Goraccin** (University of Siena, Italy), **Simone Bolognesi** (University of Siena, Italy), **Matteo Marcatili** (Dipartimento di Salute Mentale e Dipendenze ASST Monza, Italy), **Fabrizia Colmegna** (Dipartimento di Salute Mentale e Dipendenze ASST Monza, Italy), **Filippo Tati** (MDSMA Taormina-Messina Sud ASP di Messina, Italy), **Valentina Giorgelli** (Università degli Studi di Bari "Aldo Moro", Italy), **Ilaria Bufi** (Università degli Studi di Bari "Aldo Moro", Italy), **Maria Pepe** (Università Cattolica del Sacro Cuore, Rome, Italy), **Giulia Baldacci** (Department of Mental Health and Addiction Services, Niguarda Hospital, Milan and

Department of Mental Health and Addiction Services, Spedali Civili Hospital, Brescia, Italy) **Mauro Percudani** (Department of Mental Health and Addiction Services, Niguarda Hospital, Milan, Italy), **Caterina Vigano** (Department of Biomedical and Clinical Sciences Luigi Sacco University of Milan, Italy), **Beatrice Benatti** (Department of Biomedical and Clinical Sciences Luigi Sacco University of Milan, Italy), **Matteo Vismara** (Department of Biomedical and Clinical Sciences Luigi Sacco University of Milan, Italy), **Chiara Mattei** (Psychiatric Service of the Health District of Bozen, Italy), **Antonio Ventriglio** (Department of Clinical and Experimental Medicine, University of Foggia, Italy), **Ginevra Lombardozi** (Neuropsychiatric Clinic, Villa Von Siebenthal, Rome, Italy), **Eros Rossi** (Neuropsychiatric Clinic, Villa Von Siebenthal, Rome, Italy), **Maria Ilaria Scardigli** (Department of Mental Health and Addiction, ASL Roma5, Rome, Italy), **Stefania Chiappini** (Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, Chieti, Italy), **Alessio Mosca** (Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, Chieti, Italy), **Domenico de Berardis** (Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, Chieti, Italy).

*Corresponding author

Giacomo d'Andrea, MD.

Via dei Vestini 33, 66013 Chieti (CH), Italy;

Mail: giacomo.dandrea1993@gmail.com

Abstract

Background: Treatment-resistant Depression (TRD) represents a widespread disorder with significant direct and indirect healthcare costs. Esketamine, the *S*-enantiomer of ketamine, has been recently approved for TRD, but real-world studies are needed to prove its efficacy in naturalistic settings. **Objectives:** Evaluate the effectiveness and safety of Esketamine nasal spray in a clinical sample of patients with TRD from several Italian mental health services. **Methods:** REAL-ESK study is an observational, retrospective and multicentric study comprising a total of 116 TRD patients treated with Esketamine nasal spray. Anamnestic data and psychometric assessment (MADRS, HAMD-21, HAM-A) were collected from medical records at baseline (T0), one month (T1) and three month (T2) follow-ups. **Results:** A significant reduction of depressive symptoms was found at T1 and T2 compared to T0. A

dramatic increase in clinical response (64.2%) and remission rates (40.6%) was detected at T2 compared to T1. No unexpected safety concerns were observed, side effects rates were comparable to those reported in RCTs. No differences in efficacy have been found among patients with and without psychiatric comorbidities. **Limitations:** First, the open design of the study and the absence of a placebo or active comparator group are limitations. The study lacks an inter-rater reliability evaluation of the assessments among the different centres. Side effects evaluation did not involve any specific scale. **Conclusions:** Our findings support the safety and tolerability of Esketamine in a real-world TRD sample. The later response and the non-inferiority in effectiveness in patients with comorbidities represent novel and interesting findings.

Keywords: depression, esketamine, glutamate, rapid-acting, mood disorders, real-world study.

1. Introduction

Treatment-resistant depression (TRD) is prevalent, severe, and associated with considerable direct and indirect healthcare costs (Zhdanova et al., 2021) as well as high risk of suicide. The most frequently cited definition of TRD is non-remission of depressive symptoms despite two conventional monoaminergic based treatments. (McIntyre et al., 2014; Ruberto et al., 2020).

However, several lines of evidence indicates that MDD could be the result of heterogenous pathophysiological alterations (Papp et al., 2021), including glutamatergic dysfunctions (Aleksandrova et al., 2017). Reduced glutamate levels have been reported in prefrontal areas of TRD subjects (Kim & Na, 2016). Furthermore, the glutamatergic hypothesis has also been supported by the antidepressant efficacy of ketamine and esketamine, two drugs that modulate glutamatergic activity by antagonising the ionotropic N-methyl-D-aspartate (NMDA) receptor (DiazGranados et al., 2010; Zarate et al., 2006, 2012) and able to determine neuroplasticity changes via the mTOR/BDNF signalling pathways (Ardalan et al., 2020; Ricci et al., 2011).

Although limited in its clinical use due to its intravenous administration, ketamine has been demonstrated to be effective in TRD patients, with response rates ranging from 30% to 70% (Shin & Kim, 2020).

Esketamine, the *S*-enantiomer of ketamine, has recently been found to counteract treatment resistance in TRD when administered with serotonergic drugs (McIntyre et al., 2021). Its higher NMDA-receptor affinity and the intranasal formulation create the potential for esketamine to be used in outpatient settings. Based on the outcomes of several randomised trials, esketamine has been approved by the FDA and EMA as a therapeutic intervention for TRD (Daly et al., 2018; Ochs-Ross et al., 2020; Popova et al., 2019; Wajs et al., 2020). Furthermore, phase 3 RCTs have confirmed drug's safety profile, also in elderly patients (Fedgchin et al., 2019; Ochs-Ross et al., 2020; Popova et al., 2019). Among the few adverse events reported, the most common are dissociative symptoms (11.1–31.4%) characterised by the transient occurrence of changes in body perception, depersonalisation and derealisation (Swainson et al., 2019). A very low risk of abuse has been found, despite this being a potential concern (Salahudeen et al., 2020). Other transient adverse side effects reported in RCTs studies included nausea, dizziness, vertigo, hypoesthesia, sedation, paraesthesia and anxiety which were significantly increased compared with placebo (Yang et al., 2022).

Despite its well-demonstrated efficacy in experimental settings—notably, 40–50% efficacy during the maintenance phase (Wajs et al., 2020)—information about the safety and effectiveness of esketamine in naturalistic settings is still lacking. Clinical settings can include challenging TRD cases, which are usually excluded from randomised controlled trials (RCTs) (patients with substance abuse issues or patients who have commonly co-occurring physical and mental health comorbidities), which raise important safety issues and influence clinical decision-making. Hence, there are benefits to integrating information on adverse effects reported during clinical application (e.g., manic symptoms, panic attacks, ataxia and self-harm ideation) with the safety profile that emerges from RCTs.

In this observational, retrospective and multicentric study, we aimed to evaluate the effectiveness of esketamine nasal spray in a clinical sample of patients with TRD from several mental health services of different Italian regions. The purpose was to provide insights into the clinical application of esketamine as a treatment for TRD. A secondary aim was to evaluate the safety profile of esketamine in clinical settings.

2. Materials and Methods

2.1 Participants and Study Design

The REAL-ESK study was an observational, retrospective and multicentric study comprising a total of 116 patients with TRD (61 females and 55 males, with mean age = 50 ± 12 years) who were treated with esketamine nasal spray in compliance with the indications provided by the Italian regulatory agency for drugs (Agenzia Italiana del Farmaco; AIFA) and the common clinical practice of TRD management. Treatment was provided in an ‘early access’ programme that supplied esketamine to the major TRD centres in Italy.

Several Italian mental health facilities were involved in this study. The coordinating centres were the ‘G. d’Annunzio’ University of Chieti and the University of Brescia. The other centres involved were as follows: Fondazione Policlinico Universitario Agostino Gemelli IRCCS of Rome, ‘A. Moro’ University of Bari, University of Rome Tor Vergata, Sapienza University of Rome, ‘Milano Statale’ University, ‘Milano Bicocca’ University, University of Siena, ‘Magna Graecia’ University of Catanzaro, University of Pavia, University of Torino, University of Foggia, ‘Villa Maria Pia’ Clinic of Rome, ‘Von Siebenthal’ Clinic of Rome, ASL Frosinone, ASL Napoli 1, ASL Sud Tirolo, ASP Messina, ASL Umbria 2, ASL Roma 5, Department of Mental Health and Addiction Services, ASST Grande Ospedale Metropolitano ‘Niguarda’ of Milan and Villa S. Giuseppe Hospital, Ascoli Piceno.

Eligibility criteria for patients were as follows: over 18 years of age, with a major depressive episode (MDE), undergoing at least two conventional monoaminergic antidepressant trials in the absence of a clinical response (established by a qualified psychiatrist considering dose, duration, adherence and the absence of a $\geq 50\%$ decrease of depressive symptoms from baseline scale scores; TRD), and being treated with an SSRI or SNRI for which esketamine nasal spray treatment was considered appropriate, according to AIFA indications and common clinical practice of TRD management, regardless of the study.

Patients with comorbid organic pathologies (i.e., untreated arterial hypertension or previous cerebrovascular disorders) that represented an absolute contraindication to esketamine according to the AIFA were excluded from the study.

2.2 Study Procedures and Measurements

Anamnestic data were retrospectively collected and included information on sociodemographic factors, the history of depressive disease, the treatment history for the current MDE, comorbidities, antidepressant trials experienced during the lifetime, augmentation strategies (combined use of mood stabilizer/benzodiazepine/antipsychotic or not) and other therapeutic

tools applied to treat TRD. Data were also collected in case of premature study withdrawal or the occurrence of clinically relevant events, such as admission to or discharge from inpatient care, symptom relapse or MDE remission.

Anamnestic data and psychometric assessments were collected from patients' medical records at baseline (T0), one month (T1) and three months (T2) after treatment beginning.

The Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) and the Hamilton Depression Scale (HAM-D-21 items) (HAMILTON, 1960) were used to characterize depressive symptoms by clinicians. Hamilton Anxiety Rating Scale (HAM-A-21 items) (HAMILTON, 1959) was used to assess severity of anxious symptoms.

The study was approved by the local ethics committee of the Università degli studi di Brescia (Protocol Number: NP5331). All patient data were treated confidentially and anonymously, and the study was conducted in line with the Helsinki Declaration (WMA, 2013).

2.3 Statistical Analyses

Sample size was calculated using the G*Power software and the ANOVA: repeated measures, within factors test. The sample size calculation was based on an expected response to Esketamine of 40%, in line with previous findings, considering a significance level of 0.05% and a power of 95%, and with the hypothesis of a premature dropout or a non-initiation of the treatment of 20% of the patients, considering the non-experimental sample.

Statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). All tests were two-tailed, with a statistical significance level set at $p < 0.05$. Continuous variables are expressed as mean \pm standard deviation (SD), while categorical variables are reported as average numbers and percentages. Student t-test for dependent sample was conducted to assess changes in continuous variables, such as psychometric scales, from baseline (T0) to follow-up (T1 and T2), whereas Pearson χ^2 tests was performed for categorical variables.

3. Results

3.1 Baseline Characteristics and Treatments

The final analysis set included 116 patients and their sociodemographic and clinical data are extensively reported in Table 1. The analysed set was mainly composed of patients experiencing severe depression at the baseline time point. The mean MADRS score was 35 ± 8.53 , indicating severe depression (Müller et al., 2000). The majority had a history of different antidepressants trials in their lifetime (3.28 ± 1.89) and a great burden generated by their disease, as indicated by the long duration of depression (19 ± 11.05 years). Five patients (4.4%) had previously used other therapeutic tools available for treating TRD (TMS and ECT). Twenty-five patients (22.3%) had a history of suicide attempts, and the baseline MADRS item-10 mean score was 2.16 ± 1.57 , indicating moderate suicidal ideation. Personality disorders (PDs) were the most common comorbidities (15%), together with substance use disorders (SUDs; 6%), as shown in Figure 1. Most of the patients (64%) did not suffer from any other psychiatric condition. In terms of antidepressant medication, 57 patients (49.13%) were taking SSRIs, 39 patients (33.62%) were taking SNRIs and 57 patients (49.13%) were taking other antidepressants as part of augmentation strategies. Most of the patients were taking a mood stabilizer (66, 56.9%) or an antipsychotic (67, 57.7%) in addition to antidepressant (Figure 2).

3.2 One-month and Three-month Treatment Outcomes

At the one-month time point (T1), 10 of the 116 patients (8.62%) were reported as having discontinued: seven patients dropped out due to inefficacy, two dropped out due to excessive side effects during esketamine sessions and one had severe psychomotor agitation after the first session and was forced to discontinue (Table 2).

At the three-month time point (T2), a further five patients (4.31%) had discontinued esketamine use due to inefficacy. Furthermore, 10 patients had not yet reached T2 when the data analysis was conducted (Table 2).

Hence, 106 patients were included in the data analysis at T1, and 91 patients were included in the data analysis at T2.

To assess the effectiveness of esketamine use, the patients were defined as responders when they showed an overall 50% reduction in the MADRS or HAM-D-21 score compared to the baseline assessment (Fedgchin et al., 2019). In addition, remission from the current MDE was defined as a MADRS score of < 10 or a HAM-D-21 score of < 7 (Frank et al., 1991).

The Student t-test results show an overall significant reduction in MADRS scores at both T1 and T2 compared to T0. The mean MADRS score at T0 was 35 ± 8.53 , 22.27 ± 9.81 at T1 (Student t test T1 vs T0, $t= 15.79$, $gl=95$ $p < 0.0001$) and 14.69 ± 9.88 at T2 (Student t-test MADRS score T2 vs T0, $t= 18.07$, $gl=81$ $p < 0.0001$; see Figure 3). Taking esketamine was also found to have a significant effect in reducing suicidal thoughts (MADRS item-10 mean at T0 = 2.13 ± 1.58 , at T1 = 1 ± 0.55 and at T2 = 0.94 ± 0.1 ; Student t-test T1 vs T0 $t= 9.12$, $gl=95$ $p < 0.0001$, T2 vs T0 $t= 8.64$, $gl=81$ $p < 0.0001$).

Furthermore, at T1, 33 patients (28.4%) exhibited a clinical response to esketamine, while 13 patients (11.2%) were in remission from the MDE. As shown in Figure 3, at T2, increases in both clinical response (68 patients, 64.2%) and remission rate (43 patients, 40.6%) were observed (T1 responders vs. T2 responders: $\chi^2 = 12.69$ $gl=1$ $p < 0.0001$, for T1 remitters vs. T2 remitters: $\chi^2 = 12.43$ $gl=1$ $p < 0.0001$).

Interestingly, only 29% (13 patients) of T2 remitters had already reached remission at T1 (early remitters), and most of the patients (38%) who were in remission at T2 were non-responders at T1 (Figure 4).

No significant differences in sociodemographic and baseline psychometrics scores had been found between three-month responders vs non responders subjects. Even though not statistically significant, responders exhibit longer duration of the current MDE episode, with higher anxiety levels at baseline. Differences in sociodemographic and baseline psychometric measures are extensively reported in table 3.

3.3 Safety and Tolerability

Severe side effects led to the discontinuation of esketamine treatment for three patients at T1 (2.58%), as mentioned above. Notably, there was one case of severe psychomotor agitation. Dissociative symptoms (39.7%), sedation (28.4%) and transitory hypertension (10.3%) were the most common side effects reported. Manic symptoms (2.6%) and psychomotor agitation (1.7%) were infrequent, as were anxiety (2.6%) and headache (2.6%). Remarkably, 27.6% of patients reported no side effects (Figure 5).

3.4 Psychiatric Comorbidities and Add-on Therapies

In terms of global esketamine effectiveness, no significant differences were found among patients with and without any psychiatric comorbidities (Pearson's χ^2 , T1: response $p = 0.121$, remission $p = 0.339$; T2: response $p = 0.741$, remission $p = 0.257$). However, as shown in Figure 6, patients being treated with augmentation strategies that included medications other than antidepressants (i.e., antipsychotics or mood stabilizers) showed an overall lower response rate to esketamine (Pearson's χ^2 : T1 $p = 0.023$, T2 $p = 0.010$).

4. Discussion

To the best of our knowledge, this is the first study to evaluate effectiveness, safety and tolerability of esketamine for TRD in a multicentric, real-world study.

As supposed, compared to RCT samples, naturalistic and non-selected samples show higher rates of psychiatric comorbidities (15% with PDs and 6% with SUDs in our sample, both conditions represent exclusion criteria in most esketamine RCTs), longer disease duration (19 years), higher unemployment rates (48.3%) and more frequent add-on therapies (56.9% with mood stabilizers and 57.7% with antipsychotics) (Popova et al., 2019; Smith-Apeldoorn et al., 2019). Nevertheless, Esketamine determined a rapid and sustained reduction of depressive symptoms at both one-month and three-month follow-ups; the three-month response (64.2%) and remission (40.6%) rates were comparable to those reported in RCT studies (Swainson et al., 2019). These findings provide further evidence of esketamine effectiveness in TRD, providing vital proof of its potency in challenging and real-world settings.

Interestingly, we found an important difference in terms of effectiveness between the one-month and three-month follow-ups, with a dramatic increase in both the response and remission rates (remitters increased from 11.2% to 40.6% between T1 and T2). This is an important finding, since previous studies suggested that esketamine may exhibit rapid anti-TRD activity, with antidepressant activity evident within the first weeks of administration (Ionescu et al., 2021). On one hand, our study corroborates this previous finding, suggesting, on the other hand, the potential critical role of later response to esketamine.

Previous findings have suggested that the *induction phase* (the first month) is the key period for evaluating the therapeutic benefit of esketamine (Turkoz et al., 2021). This was confirmed by the *sustain study*, in which a reduction of depressive symptoms was reported within the first month and perpetrated during 48 weeks of maintenance (Wajs et al., 2020). In contrast with these findings, most of our three-month remitters were not responders at one month (38%),

indicating that the induction phase should not be the sole evaluation period for esketamine efficacy. This finding has significant implications for clinicians: continuing esketamine treatment beyond the induction phase could result in a later successful response (71% of remitters were not remitters at T1).

The differences between our findings and previous ones are intriguing and allow some speculation. Our clinical sample contained patients with more severe depressive symptoms and associated factors than those recruited for RCTs. The symptoms of our patients partly resembled refractory depressive episodes rather than TRD. Therefore, the later response observed in our study could be due to the baseline clinical presentation of our sample, and this may shed light on the possible mechanism responsible for the efficacy of the esketamine treatment.

Both ketamine and esketamine increase brain plasticity in glutamatergic synapses involving the mTOR/BDNF signaling pathways (Ardalan et al., 2020; Ricci et al., 2011). Esketamine-induced plasticity phenomena implicated synaptic long-term potentiation (LTP), which could be responsible of its antidepressant action. In our sample, characterized by higher burden disease, frequent comorbidity and longer disease duration, antidepressant effects related to esketamine-induced LTP could request longer time of exposure, thus explaining the increased latency of response.

Another possible explanation pertains to the low number of subjects prescribed with the 83 mg since the first weeks of treatment (notably, a large proportion of subject switch from 56 to 84 mg dosage after T1, as shown by the increase of 84 mg dosage from 26.5% - T1- to the 38.5% of the sample -T2-, see table 1). Often clinicians in real-life settings, especially with the first patients, tend to be rather cautious, particularly with elderly subjects, increasing the dosage in few cases and after a substantial amount of time. This strategy may have delayed the effect, determining an initial latency. Moreover, in real-life settings compliance is usually inferior to what is commonly observed in clinical trials, where patients are paid and/or strongly motivated to attend by the clinical staff. A reduction in compliance could be considered as another aspect able to reduce an early response since the first weeks of treatment.

Generally, esketamine appears to be a safe and tolerable treatment in our clinical study: no new or unexpected safety concerns were observed, and side effects rates were comparable to those reported in RCT studies (Swainson et al., 2019). Manic symptoms, which were a potential

concern in clinical settings (Yang et al., 2022), were uncommon (2.6%) and time dependent. Furthermore, no maniacal switch or any addictive issues (craving, withdrawal symptoms) have been reported.

Undoubtedly, esketamine may be a challenging treatment, considering the needs for patients of repeated visits for the administrations and direct healthcare supervision (Swainson et al., 2019). These conditions increase the risk of lower adherence to treatment in common clinical practice (Salahudeen et al., 2020). Despite these potential concerns, dropout rates in our study were very low at both one-month (8.62%) and three-month (4.31%) follow-ups, indicating good adherence and retention in the treatment programme.

As previously mentioned, most esketamine RCTs exclude patients with co-occurring psychiatric disorders, such as OCD, SUDs or PDs (Capuzzi et al., 2021). However, our clinical study obviously involved patients with co-occurring psychiatric disorders, and the most frequent were PDs (15%) and SUDs (6%). Surprisingly, our findings demonstrate the non-inferiority of esketamine use in terms of effectiveness and safety in those affected by other psychiatric conditions. This is an intriguing finding, since comorbidity is one of the most important concerns in MDD and a significant cause of treatment resistance (Gaynes, 2016). These findings also provide new perspectives and potential clinical applications of esketamine use, as highlighted in previous studies (Martinotti et al., 2021).

Furthermore, treatment resistance is usually related to the use of an augmentation strategy, such as mood-stabilizer and antipsychotic medications (Cantù et al., 2021; Nuñez et al., 2022). In our clinical study, most of the patients were using a mood stabilizer (56.9%) or an antipsychotic (57.7%) during the treatment period. Interestingly, esketamine effectiveness was lower in patients who were being treated with mood stabilizers or antipsychotics compared to those who were not. This finding could be explained in two different ways: on one hand, the lower effectiveness could have been related to the higher severity of the depression experienced by those patients treated with augmentation strategies. On the other hand, pharmacodynamic interactions between esketamine and mood stabilizers or antipsychotics may have influenced the treatment outcomes by reducing the overall antidepressant effect, as previously evidenced in ketamine studies (Veraart et al., 2021). Further studies are necessary to examine the impact of different molecules (e.g., lithium, valproate, lamotrigine and atypical antipsychotics) on esketamine efficacy.

Our findings should be interpreted cautiously due to several limitations. First, the open design of the study and the absence of a placebo or active comparator group are limitations. The study lacks an inter-rater reliability evaluation of the psychometric assessments among the different centres involved, which could have determined differences in the evaluation methods and scoring of TRD. Second, the evaluation of side effects did not involve any structured or semi-structured interviews or any specific assessment scale; instead, data were extracted from patients' clinical records for the evaluation of side effects.

Nevertheless, our study has major strengths. These include the involvement of several different mental health facilities across various Italian regions and the use of a clinical sample. This could be considered a limitation due to the restricted generalisability of the results; however, using a clinical sample bridges the gap between RCTs and real-world situations. Patients included in TRD RCTs are poorly representative of the treatment-seeking depressive patients treated in routine clinical practice, and using a clinical sample provides valuable data on outcomes in real-world situations.

5. Conclusions

Our observational data support the safety and tolerability of esketamine in a real-world sample of adults with TRD. Our data also indicate clinical effectiveness of esketamine in this population. The later response, as well as the non-inferiority in effectiveness in patients with comorbidities represent novel and interesting findings. There were no evidence of abuse, misuse, withdrawal, gateway activity, and no long term cognitive or urogenital or hepatic toxicity, as previously documented for ketamine (Le et al., 2022; Ng et al., 2021). Our findings, although limited by the open design of the study, supplement RCTs data, suggesting esketamine as an important option in the algorithmic treatment of persons with TRD.

6. Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

7. Acknowledgments

This work was supported by the “Departments of Excellence 2018–2022” initiative of the Italian Ministry of Education, University and Research for the Department of Neuroscience, Imaging and Clinical Sciences (DNISC) of the University of Chieti-Pescara.

The authors wish to thank dr. Dario Delmonte and dr. Giuseppe Ascione for their contribution in the coordination of the different clinical centers involved in the study and for their scientific support in the literature review.

8. Potential Conflict of Interests

Giovanni Martinotti has been a consultant and/or a speaker and/or has received research grants from Angelini, Doc Generici, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Servier and Recordati. Alessandro Bertolino and Ileana Andriola were both speakers at Janssen-sponsored conference.

Andrea Fagiolini has been a consultant and/or a speaker and/or has received research grants from Allergan, Angelini, Apsen, Boehringer Ingelheim, Doc Generici, FB-Health, Italfarmaco, Janssen, Lundbeck, Mylan, Otsuka, Pfizer, Recordati, Sanofi Aventis, Sunovion, Vifor.

Bernardo Dell’Osso has received lecture honoraria from Angelini, Lundbeck, Janssen, Pfizer, Neuraxpharm, Arcapharma, and Livanova.

Massimo di Giannantonio has been a consultant and/or a speaker and/or has received research grants from Angelini, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Servier, Recordati.

Antonio Vita received grant/research support and speaker/consultant fees for Angelini, Boheringer Ingelheim, Innovapharma, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Recordati, Roche, Rovi Pharma, Takeda.

Giuseppe Maina has been a consultant/speaker for Angelini, Boheringer, Fb Health, Innovapharma, Italfarmaco, Janssen, Otsuka, Lundbeck, Sanofi.

Gabriele Sani has been a consultant/speaker for Angelini, Fb Health, Italfarmaco, Janssen, Otsuka, Lundbeck, Sanofi.

Roger McIntyre has received grant/research support from CIHR/GACD/ Chinese National Natural Research Foundation and speaking or consultation fees from AbbVie, Bausch Health, Eisai, Intra-Cellular, Janssen, Kris, Lundbeck, Minerva, Neurocrine, Novo Nordisk, Eli Lilly, Otsuka, Pfizer, Purdue, Sunovion, and Takeda; he is also the CEO of Champignon Brands, Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

9. Authors Statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

MdG, AVi, GMar, GMai, ABer, AF, SB and MP conceptualized the hypothesis and the design of the study.

GMar, SB, BDO, AS, ABell, MC, GS, MdN, RDC, GDL, PDF, SDF, GN, GRo, AValc, DN, SDM, RB, VM, AC, IA, MO and SBel were responsible for the patient recruitment and the collection of clinical data.

The REAL-ESK Study Group contributed to the collection of clinical data.

GdA, GMar and MP performed the statistical analysis, carried out data interpretation and wrote the first draft of the manuscript.

MdG, AVi, AF, GDL, ABer, BDO and RSMcI revised the manuscript and provided substantial comments.

All authors have contributed to, and have approved, the final manuscript.

Table 1. Sociodemographic and clinical data.

	<i>Mean</i>	<i>SD</i>
<i>Age</i>	50	12.45
<i>Education (years)</i>	12.9	4.4
<i>MDE duration (months)</i>	16.5	6.4
<i>Age at onset of depression (years)</i>	31.59	12.71
<i>Number of previous EDM (n)</i>	3.85	2.85
<i>Duration of depression (years)</i>	19	11.05
<i>Number of adequate antidepressant trials lifetime (n)</i>	3.28	1.89
<i>Baseline clinical measures</i>		
<i>MADRS</i>	35	8.53
<i>HAM-D, 21 item</i>	27.7	8.48
<i>HAM-A</i>	25.42	11.91
<i>Suicidality: MADRS item 10</i>	2.16	1.57
	N	%
<i>Female</i>	61	52.6
<i>Esketamine Dosage</i>		
<i>1-Month (n=106)</i>		
<i>28 mg</i>	8	7.5
<i>56 mg</i>	70	66

<i>84 mg</i>	28	26.5
<i>3-Month (n=91)</i>		
<i>28 mg</i>	8	8.8
<i>56 mg</i>	48	52.7
<i>84 mg</i>	35	38.5
<i>Status</i>		
<i>Single</i>	44	37.9
<i>Married</i>	59	50.9
<i>Divorced /widowed</i>	13	11.2
<i>Occupation</i>		
<i>Unemployed</i>	56	48.3
<i>Employed</i>	60	51.7
<i>Previous Suicidal Attempts?</i>		
<i>No</i>	87	77.7
<i>Yes</i>	25	22.3
<i>Participants who attempted FDA-approved rTMS</i>	4	3.5
<i>Participants who attempted ECT</i>	1	0.9

Table 2. Drop-out rates

	<i>N</i>	<i>%</i>
<i>Drop out rates</i>		
<i>1-month</i>	10	8.62
<i>Side effects</i>	2	1.72
<i>Severe psychomotor agitation</i>	1	0.86
<i>Low effect</i>	7	6.03
<i>3-month</i>	5	4.31
<i>Low effect</i>	5	4.31
<i>Total Drop-out</i>	15	12.93
<i>Patients still not at T2</i>	10	8.62

Table 3. Differences between 3-months responders and non-responders in sociodemographic and baseline psychometric scores.

	<i>3-month responders (n=68)</i>	<i>3-month non responders (n=23)</i>
<i>Gender (n)</i>	male: 33 female: 35	male :10 female :13
<i>Age</i>	50.66 ± 13.46	50.47 ± 8.24
<i>Status</i>		
<i>Single</i>	25	8
<i>Married</i>	36	11
<i>Divorced /widowed</i>	7	4
<i>Education (years)</i>	12.03 ± 4.52	13.78 ± 4.72
<i>Occupation</i>		
<i>Unemployed</i>	36	9
<i>Employed</i>	32	14
<i>MDE duration (months)</i>	18.72 ± 12.93	15.87 ± 12.69
<i>Age at onset of depression (years)</i>	31 ± 13.65	31.6 ± 12
<i>Number of previous EDM (n)</i>	3.73 ± 2.87	4 ± 3.15
<i>Duration of depression (years)</i>	18.66 ± 11.30	18.86 ± 12.1
<i>Number of adequate antidepressant trials lifetime (n)</i>	3.42 ± 0.51	3.25 ± 0.71
<i>Baseline clinical measures</i>		
<i>MADRS</i>	35.37 ± 8.61	35.9 ± 9.94
<i>HAM-D, 21 item</i>	28.5 ± 8.32	27.3 ± 9.46

<i>HAM-A</i>	28.34 ± 11.65	23.52 ± 14.76
<i>Previous Suicidal Attempts?</i>		
<i>No</i>	49	16
<i>Yes</i>	17	5

Fig 1. Psychiatric Comorbidities. GAD: General Anxiety Disorder; OCD: Obsessive-Compulsive Disorder; ED= Eating Disorders; PTSD: Post-traumatic Stress Disorder; SUD: Substance Use Disorder

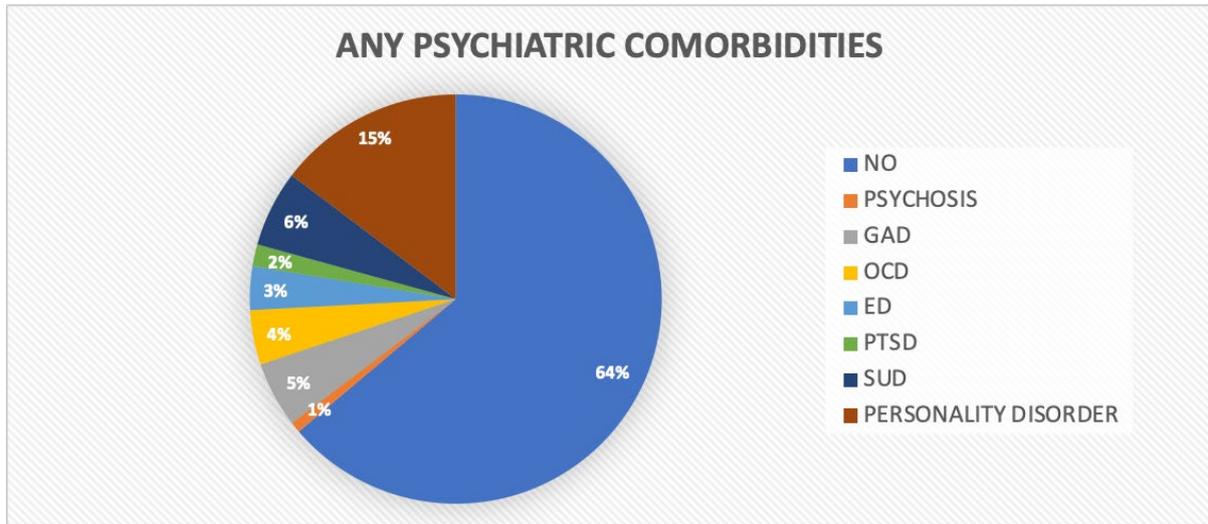


Fig 2. Add-on therapies. SSRI: Selective serotonin reuptake inhibitors; SNRI: serotonin and norepinephrine reuptake inhibitors.

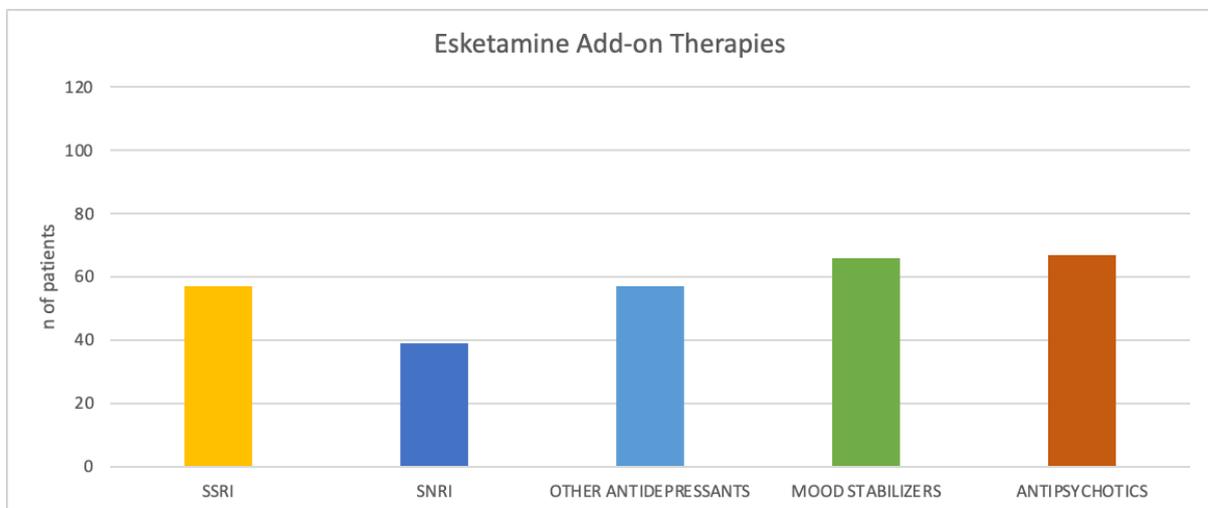


Fig. 3: Treatment outcomes. MADRS: Montgomery-Asberg Depression Rating Scale

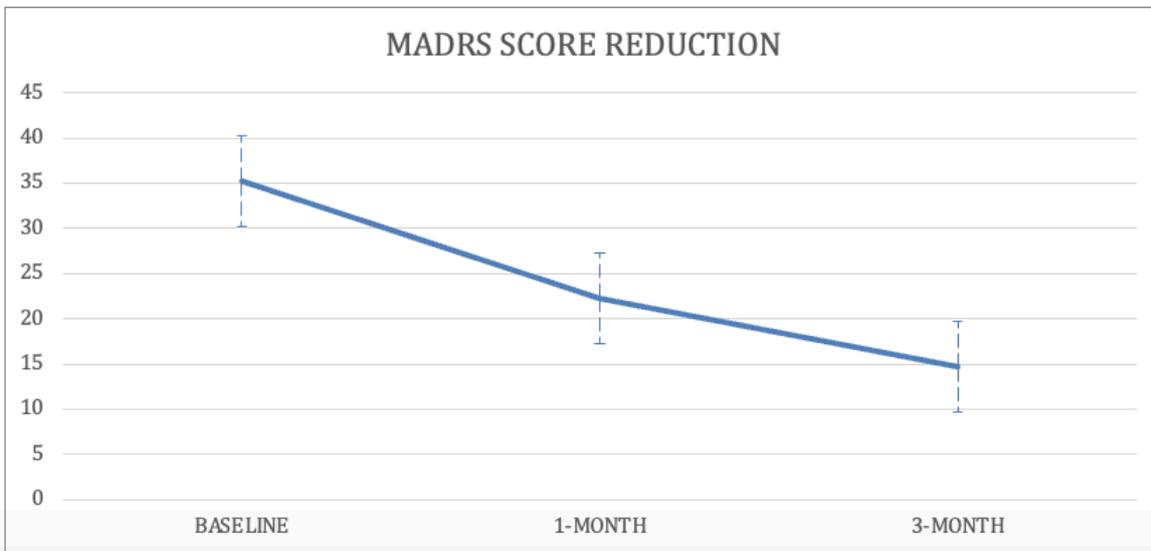
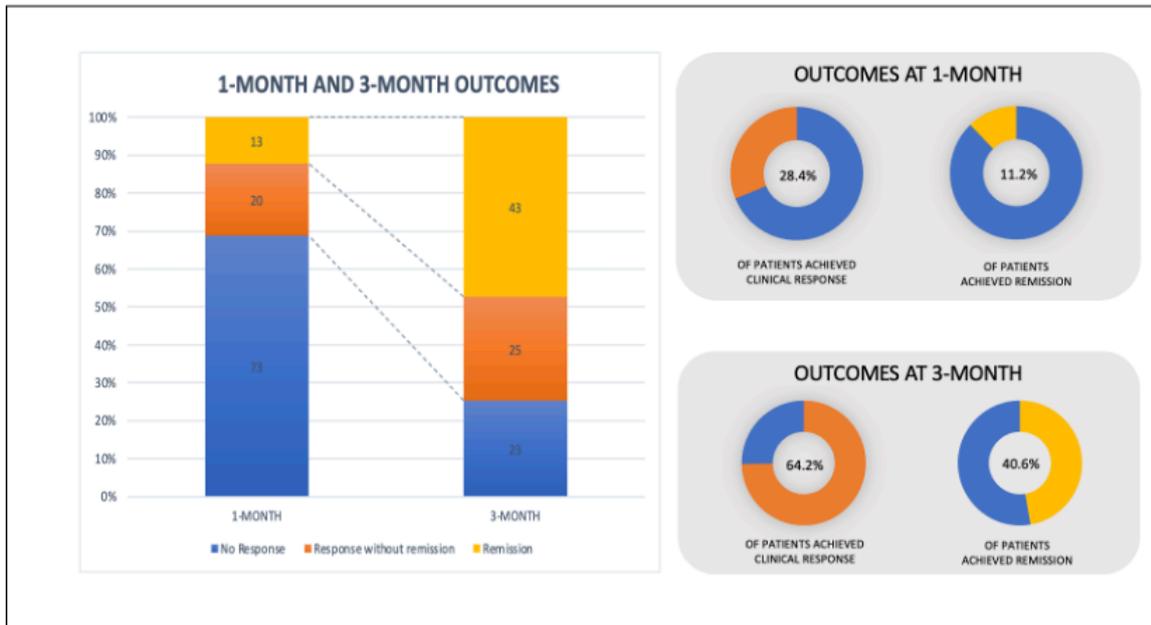


Fig. 4. 3-month remitters at 1-month.

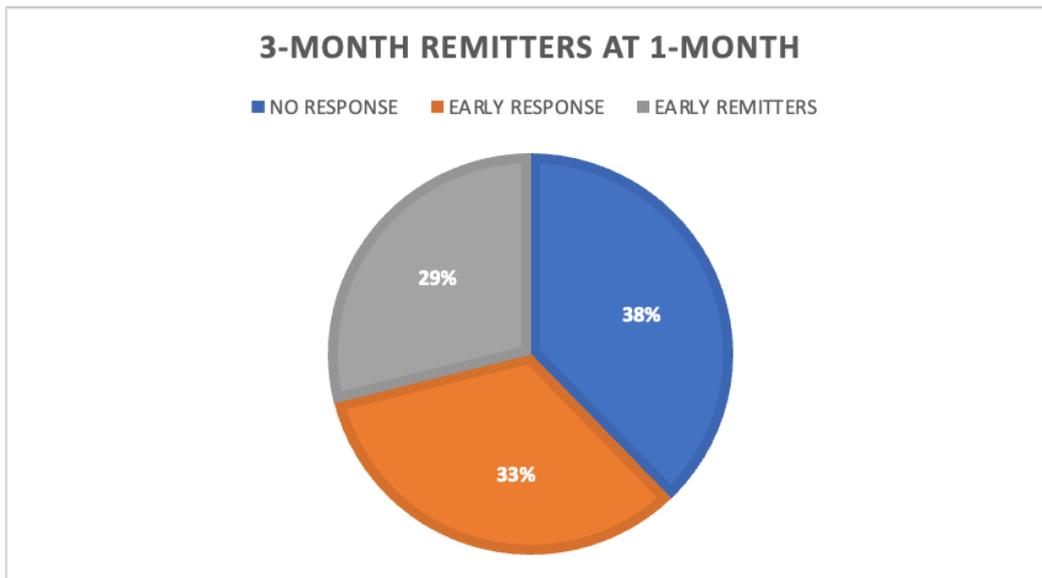


Fig.5 Reported Side Effects.

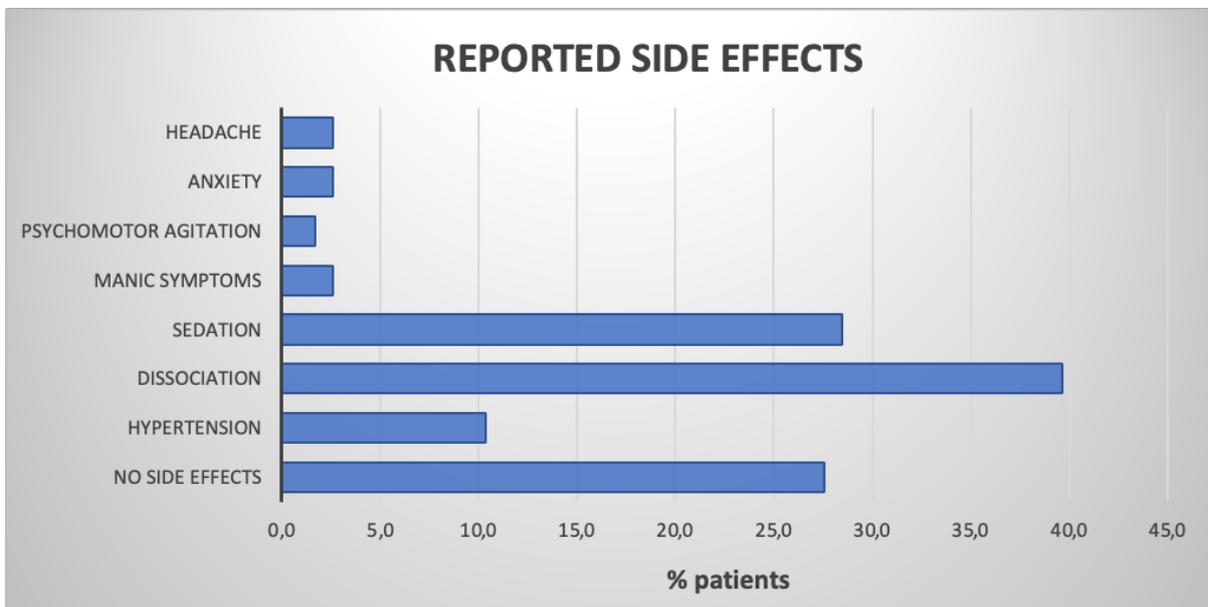
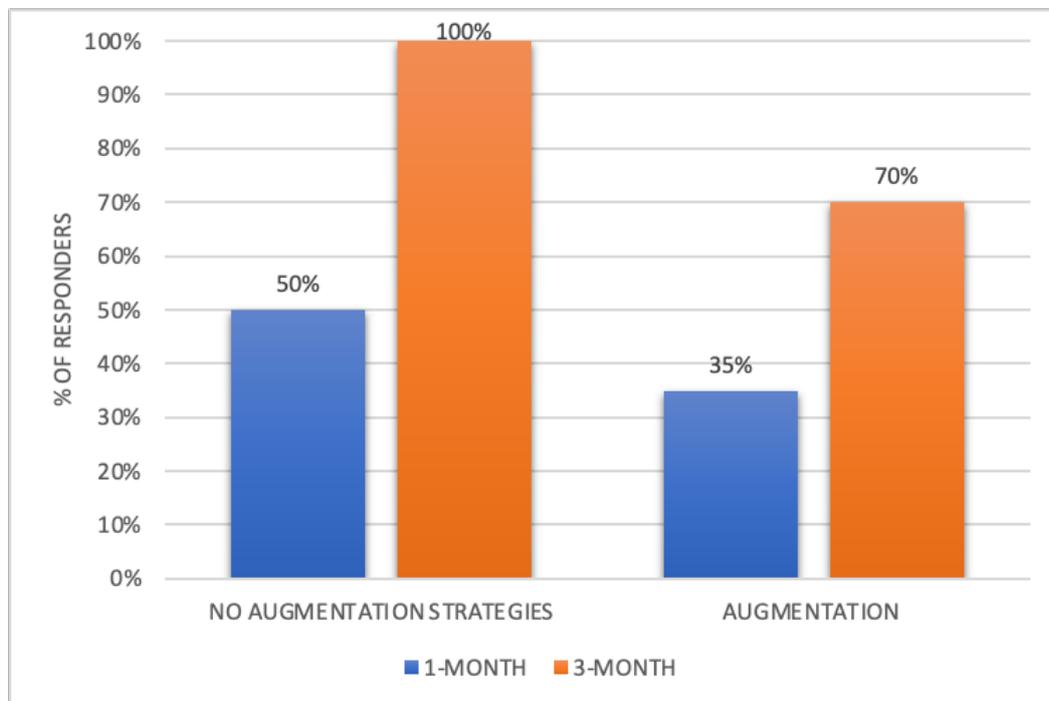


Fig.6 Differences in % of responders with or without augmentation strategies (mood stabilizer or antipsychotics)



References

- Aleksandrova, L. R., Phillips, A. G., & Wang, Y. T. (2017). Antidepressant effects of ketamine and the roles of AMPA glutamate receptors and other mechanisms beyond NMDA receptor antagonism. *Journal of Psychiatry and Neuroscience*, *42*(4), 222–229. <https://doi.org/10.1503/jpn.160175>
- Ardalan, M., Elfving, B., Rafati, A. H., Mansouri, M., Zarate, C. A., Mathe, A. A., & Wegener, G. (2020). Rapid effects of S-ketamine on the morphology of hippocampal astrocytes and BDNF serum levels in a sex-dependent manner. *European Neuropsychopharmacology*, *32*, 94–103. <https://doi.org/https://doi.org/10.1016/j.euroneuro.2020.01.001>
- Cantù, F., Ciappolino, V., Enrico, P., Moltrasio, C., Delvecchio, G., & Brambilla, P. (2021). Augmentation with Atypical Antipsychotics for Treatment-Resistant Depression. *Journal of Affective Disorders*, *280*, 45–53. <https://doi.org/https://doi.org/10.1016/j.jad.2020.11.006>
- Capuzzi, E., Caldiroli, A., Capellazzi, M., Tagliabue, I., Marcatili, M., Colmegna, F., Clerici, M., Buoli, M., & Dakanalis, A. (2021). Long-Term Efficacy of Intranasal Esketamine in Treatment-Resistant Major Depression: A Systematic Review. *International Journal of Molecular Sciences*, *22*(17). <https://doi.org/10.3390/ijms22179338>
- Daly, E. J., Singh, J. B., Fedgchin, M., Cooper, K., Lim, P., Shelton, R. C., Thase, M. E., Winokur, A., Van Nueten, L., Manji, H., & Drevets, W. C. (2018). Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: A randomized clinical trial. *JAMA Psychiatry*, *75*(2), 139–148. <https://doi.org/10.1001/jamapsychiatry.2017.3739>
- DiazGranados, N., Ibrahim, L. A., Brutsche, N. E., Ameli, R., Henter, I. D., Luckenbaugh, D. A., Machado-Vieira, R., & Zarate, C. A. J. (2010). Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *The Journal of Clinical Psychiatry*, *71*(12), 1605–1611. <https://doi.org/10.4088/JCP.09m05327blu>
- Fedgchin, M., Trivedi, M., Daly, E. J., Melkote, R., Lane, R., Lim, P., Vitagliano, D., Blier, P., Fava, M., Liebowitz, M., Ravindran, A., Gaillard, R., Ameele, H. Van Den, Preskorn, S., Manji, H., Hough, D., Drevets, W. C., & Singh, J. B. (2019). Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-

- Blind, Active-Controlled Study (TRANSFORM-1). *International Journal of Neuropsychopharmacology*, 22(10), 616–630. <https://doi.org/10.1093/ijnp/pyz039>
- Frank, E., Prien, R. F., Jarrett, R. B., Keller, M. B., Kupfer, D. J., Lavori, P. W., Rush, A. J., & Weissman, M. M. (1991). Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Archives of General Psychiatry*, 48(9), 851–855. <https://doi.org/10.1001/archpsyc.1991.01810330075011>
- Gaynes, B. (2016). Assessing the risk factors for difficult-to-treat depression and treatment-resistant depression. *The Journal of Clinical Psychiatry*, 77 Suppl 1, 4–8. <https://doi.org/10.4088/JCP.14077su1c.01>
- HAMILTON, M. (1959). The assessment of anxiety states by rating. *The British Journal of Medical Psychology*, 32(1), 50–55. <https://doi.org/10.1111/j.2044-8341.1959.tb00467.x>
- HAMILTON, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, 23(1), 56–62. <https://doi.org/10.1136/jnnp.23.1.56>
- Ionescu, D. F., Fu, D.-J., Qiu, X., Lane, R., Lim, P., Kasper, S., Hough, D., Drevets, W. C., Manji, H., & Canuso, C. M. (2021). Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). *The International Journal of Neuropsychopharmacology*, 24(1), 22–31. <https://doi.org/10.1093/ijnp/pyaa068>
- Kim, Y.-K., & Na, K.-S. (2016). Role of glutamate receptors and glial cells in the pathophysiology of treatment-resistant depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 70, 117–126. <https://doi.org/https://doi.org/10.1016/j.pnpbp.2016.03.009>
- Le, T. T., Pazos, I., Youshay, M., Swainson, J., Di, J. D., Jaber, S., Phan, L., Lui, L. M. W., Ho, R., Rosenblat, J. D., & McIntyre, R. S. (2022). The abuse liability of ketamine : A scoping review of preclinical and clinical studies. *Journal of Psychiatric Research*, 151(April), 476–496. <https://doi.org/10.1016/j.jpsychires.2022.04.035>
- Martinotti, G., Chiappini, S., Pettorruso, M., Mosca, A., Miuli, A., Di Carlo, F., D’Andrea, G., Collecchio, R., Di Muzio, I., Sensi, S. L., & Di Giannantonio, M. (2021). Therapeutic Potentials of Ketamine and Esketamine in Obsessive-Compulsive Disorder (OCD), Substance Use Disorders (SUD) and Eating Disorders (ED): A Review of the Current Literature. *Brain Sciences*, 11(7). <https://doi.org/10.3390/brainsci11070856>
- McIntyre, R. S., Filteau, M.-J., Martin, L., Patry, S., Carvalho, A., Cha, D. S., Barakat, M., &

- Migueluez, M. (2014). Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *Journal of Affective Disorders, 156*, 1–7. <https://doi.org/10.1016/j.jad.2013.10.043>
- McIntyre, R. S., Rosenblat, J. D., Nemeroff, C. B., Sanacora, G., Murrough, J. W., Berk, M., Brietzke, E., Dodd, S., Gorwood, P., Ho, R., Iosifescu, D. V., Jaramillo, C. L., Kasper, S., Kratiuk, K., Lee, J. G., Lee, Y., Lui, L. M. W., Mansur, R. B., Papakostas, G. I., ... Stahl, S. (2021). Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: An international expert opinion on the available evidence and implementation. *American Journal of Psychiatry, 178*(5), 383–399. <https://doi.org/10.1176/appi.ajp.2020.20081251>
- Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry: The Journal of Mental Science, 134*, 382–389. <https://doi.org/10.1192/bjp.134.4.382>
- Müller, M. J., Szegedi, A., Wetzel, H., & Benkert, O. (2000). Moderate and severe depression. Gradations for the Montgomery-Asberg Depression Rating Scale. *Journal of Affective Disorders, 60*(2), 137–140. [https://doi.org/10.1016/s0165-0327\(99\)00162-7](https://doi.org/10.1016/s0165-0327(99)00162-7)
- Ng, J., Lui, L. M. W., Rosenblat, J. D., Teopiz, K. M., Lipsitz, O., Cha, D. S., Xiong, J., Nasri, F., Lee, Y., Kratiuk, K., Rodrigues, N. B., Gill, H., Subramaniapillai, M., Mansur, R. B., Ho, R., Cao, B., & McIntyre, R. S. (2021). Ketamine-induced urological toxicity: potential mechanisms and translation for adults with mood disorders receiving ketamine treatment. *Psychopharmacology, 238*(4), 917–926. <https://doi.org/10.1007/s00213-021-05767-1>
- Nuñez, N. A., Joseph, B., Pahwa, M., Kumar, R., Resendez, M. G., Prokop, L. J., Veldic, M., Seshadri, A., Biernacka, J. M., Frye, M. A., Wang, Z., & Singh, B. (2022). Augmentation strategies for treatment resistant major depression: A systematic review and network meta-analysis. *Journal of Affective Disorders, 302*, 385–400. <https://doi.org/https://doi.org/10.1016/j.jad.2021.12.134>
- Ochs-Ross, R., Daly, E. J., Zhang, Y., Lane, R., Lim, P., Morrison, R. L., Hough, D., Manji, H., Drevets, W. C., Sanacora, G., Steffens, D. C., Adler, C., McShane, R., Gaillard, R., Wilkinson, S. T., & Singh, J. B. (2020). Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression—TRANSFORM-3. *American Journal of Geriatric Psychiatry, 28*(2), 121–141. <https://doi.org/10.1016/j.jagp.2019.10.008>
- Papp, M., Cubala, W. J., Swiecicki, L., Newman-Tancredi, A., & Willner, P. (2021).

- Perspectives for therapy of treatment-resistant depression. *British Journal of Pharmacology*. <https://doi.org/10.1111/bph.15596>
- Popova, V., Daly, E. J., Trivedi, M., Cooper, K., Lane, R., Lim, P., Mazzucco, C., Hough, D., Thase, M. E., Shelton, R. C., Molero, P., Vieta, E., Bajbouj, M., Manji, H., Drevets, W. C., & Singh, J. B. (2019). Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: A randomized double-blind active-controlled study. *American Journal of Psychiatry*, *176*(6), 428–438. <https://doi.org/10.1176/appi.ajp.2019.19020172>
- Ricci, V., Martinotti, G., Gelfo, F., Tonioni, F., Caltagirone, C., Bria, P., & Angelucci, F. (2011). Chronic ketamine use increases serum levels of brain-derived neurotrophic factor. *Psychopharmacology*, *215*(1), 143–148. <https://doi.org/10.1007/s00213-010-2121-3>
- Ruberto, V. L., Jha, M. K., & Murrrough, J. W. (2020). Pharmacological Treatments for Patients with Treatment-Resistant Depression. *Pharmaceuticals*, *13*(6). <https://doi.org/10.3390/ph13060116>
- Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J., & Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *The American Journal of Psychiatry*, *163*(11), 1905–1917. <https://doi.org/10.1176/ajp.2006.163.11.1905>
- Salahudeen, M. S., Wright, C. M., & Peterson, G. M. (2020). Esketamine: new hope for the treatment of treatment-resistant depression? A narrative review. *Therapeutic Advances in Drug Safety*, *11*, 2042098620937899. <https://doi.org/10.1177/2042098620937899>
- Shin, C., & Kim, Y.-K. (2020). Ketamine in Major Depressive Disorder: Mechanisms and Future Perspectives. *Psychiatry Investig*, *17*(3), 181–192. <https://doi.org/10.30773/pi.2019.0236>
- Smith-Apeldoorn, S. Y., Veraart, J. K. E., Kamphuis, J., van Asselt, A. D. I., Touw, D. J., aan het Rot, M., & Schoevers, R. A. (2019). Oral esketamine for treatment-resistant depression: rationale and design of a randomized controlled trial. *BMC Psychiatry*, *19*(1), 375. <https://doi.org/10.1186/s12888-019-2359-1>
- Swainson, J., Thomas, R. K., Archer, S., Chrenek, C., MacKay, M.-A., Baker, G., Dursun, S., Klassen, L. J., Chokka, P., & Demas, M. L. (2019). Esketamine for treatment resistant depression. *Expert Review of Neurotherapeutics*, *19*(10), 899–911.

<https://doi.org/10.1080/14737175.2019.1640604>

Turkoz, I., Daly, E., Singh, J., Lin, X., Tymofyeyev, Y., Williamson, D., Salvatore, G., Nash, A. I., Macaluso, M., Wilkinson, S. T., & Nelson, J. C. (2021). Treatment Response With Esketamine Nasal Spray Plus an Oral Antidepressant in Patients With Treatment-Resistant Depression Without Evidence of Early Response: A Pooled Post Hoc Analysis of the TRANSFORM Studies. *The Journal of Clinical Psychiatry*, *82*(4).

<https://doi.org/10.4088/JCP.20m13800>

Veraart, J. K. E., Smith-Apeldoorn, S. Y., Bakker, I. M., Visser, B. A. E., Kamphuis, J., Schoevers, R. A., & Touw, D. J. (2021). Pharmacodynamic Interactions Between Ketamine and Psychiatric Medications Used in the Treatment of Depression: A Systematic Review. *The International Journal of Neuropsychopharmacology*, *24*(10), 808–831. <https://doi.org/10.1093/ijnp/pyab039>

Wajs, E., Aluisio, L., Holder, R., Daly, E. J., Lane, R., Lim, P., George, J. E., Morrison, R. L., Sanacora, G., Young, A. H., Kasper, S., Sulaiman, A. H., Li, C.-T., Paik, J.-W., Manji, H., Hough, D., Grunfeld, J., Jeon, H. J., Wilkinson, S. T., ... Singh, J. B. (2020). Esketamine Nasal Spray Plus Oral Antidepressant in Patients With Treatment-Resistant Depression: Assessment of Long-Term Safety in a Phase 3, Open-Label Study (SUSTAIN-2). *The Journal of Clinical Psychiatry*, *81*(3).

<https://doi.org/10.4088/JCP.19m12891>

WMA. (2013). Dichiarazione di Helsinki della World Medical Association. *Evidence*, *5*(10), 1–5.

Yang, S., Wang, J., Li, X., Wang, T., Xu, Z., Xu, X., Zhou, X., & Chen, G. (2022). Adverse Effects of Esketamine for the Treatment of Major Depression Disorder: Findings from Randomized Controlled Trials. *The Psychiatric Quarterly*, *93*(1), 81–95.

<https://doi.org/10.1007/s11126-020-09871-x>

Zarate, C. A. J., Brutsche, N. E., Ibrahim, L., Franco-Chaves, J., Diazgranados, N., Cravchik, A., Selter, J., Marquardt, C. A., Liberty, V., & Luckenbaugh, D. A. (2012). Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biological Psychiatry*, *71*(11), 939–946.

<https://doi.org/10.1016/j.biopsych.2011.12.010>

Zarate, C. A. J., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., Charney, D. S., & Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry*, *63*(8), 856–864. <https://doi.org/10.1001/archpsyc.63.8.856>

Zhdanava, M., Pilon, D., Ghelerter, I., Chow, W., Joshi, K., Lefebvre, P., & Sheehan, J. J. (2021). The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. *The Journal of Clinical Psychiatry*, 82(2). <https://doi.org/10.4088/JCP.20m13699>