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Esketamine in treatment resistant depression: a study protocol for a retrospective, real-life, multicentric study

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Background

Major Depressive Disorder (MDD) is a common psychiatric disorder that impairs psychosocial functioning and limits the quality of life of those affected. Currently, mood disorders determine significant costs, amounting to 113.4 billion euros in Europe, with 37% of direct costs related to psychiatric treatments and 63% related to indirect social costs [1]. Furthermore, WHO ranked MDD as the third largest cause of global health expenditure on disease and predicted that it will be the first by 2030 [2].

MDD is a highly heterogeneous diagnostic entity that includes various and recurrent symptoms with clinical manifestations that could be supported by different pathophysiological mechanisms. Over the years, the clinical heterogeneity of depression has led to different attempts to define clinical subtypes of MDD to improve the diagnosis and treatment of this disorder. To date, however, we are still far from a correct categorization of the depressive universe in all its different clinical manifestations and from a correct subtyping that takes into account the different neurobiological mechanisms underlying MDD. Due to the clinical heterogeneity of depression, approximately 30-50% of patients do not respond to first-line therapies, experimenting treatment-resistant depression (TRD) [3], defined as the absence of a clinical response to two antidepressants of appropriate dose and duration (≥ 4-6 weeks) [4].

An open question concerns the substrates underlying this clinical heterogeneity and high rates of TRD. Conventional antidepressant treatments target the

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Conflict of interest
The authors declare that they have no conflict of interest nor that they have received compensation from third parties for the creation of this article.

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monoaminergic systems, which are thought to be the neurobiological substrates of depression. According to this hypothesis, depressive symptoms are associated with dysfunction of the dopamine, norepinephrine, and serotonin systems [5]. However, the absence of a clinical response to conventional antidepressant in a consistent part of MDD subjects suggests that a non-monoaminergic etiology may underlie TRD [6].

In light of this, several studies have focused on the role of glutamatergic neurotransmission in depressive disorders as a potential therapeutic target in TRD [7,8]. Glutamate plays a crucial role in synaptic transmission and neuronal plasticity, being involved in brain areas implicated in mood and affectivity [7]. Several neuroimaging studies have shown significant reductions in glutamate levels in unipolar depression in the anterior cingulate cortex and parietal white matter [9-11]. Furthermore, glutamatergic activity is reduced in the dorsolateral prefrontal cortical area (DLPFC) and in the dorsomedial and ventromedial anterolateral prefrontal areas in patients with TRD [12].

Besides, some studies have found normal or increased glutamate levels in patients who were in remission after electroconvulsive therapy [13,14], suggesting that glutamate levels can be rebalanced by treatments with proven antidepressant efficacy [15,16].

The relevance of glutamatergic activity in TRD is also supported by the antidepressant action of molecules with glutamatergic activity such as ketamine, an NMDA receptor antagonist [17], widely investigated by several studies [18,19]. Ketamine, despite its efficacy, remains a complex treatment due to the challenging management of the intravenous formulation and the significant risk of side effects [20].

Given the evidence supporting the glutamatergic hypothesis, a new therapeutic option for the treatment of TRD has recently been approved by the Italian Medicines Agency (AIFA): Esketamine nasal spray.

Esketamine (the S-enantiomer) shows a NMDA antagonism stronger than ketamine itself, [21] with lower side effects rates [22]. The antidepressant efficacy of esketamine has been demonstrated in several studies [23-25], with data indicating a remission rate greater than 50% in TRD [26]. A randomized clinical trial (RCT) showed significant improvement in depressive symptoms in patients treated with esketamine along with an oral antidepressant, lasting up to 52 weeks [26].

Esketamine also showed a favorable safety profile with few serious adverse events (less than 5%) in pivotal studies [22]. The most common adverse effects include dissociative symptoms (affecting between 11.1 and 31.4% of subjects in pivotal trials) [22], such as changes in body perception, depersonalization, and derealization [21].

Although previous findings show the good efficacy and tolerability of esketamine in TRD, real-world studies are needed to validate the results observed in RCTs in patients' samples from the general practice.

Furthermore, given the extreme clinical heterogeneity of both TRD and MDD, studies investigating clinical phenotypes, based on psychopathological and anamnestic data, more likely to respond to Esketamine are necessary. Finding valuable clinical markers of response to Esketamine would have a significant impact in clinical practice, reducing healthcare costs and limiting failed antidepressant trials.

Aims of the study

Considering previous evidences, the main aim of this study is:

- to evaluate efficacy of Esketamine nasal spray treatment in a clinical and non-experimental sample of TRD patients, estimating the reduction of depressive symptoms at one month (T1) and at three months (T2), highlighting its safety and tolerability.

Secondary aims of the study are:

- to investigate clinical TRD subphenotypes more responsive to Esketamine through anamnestic data and psychometric scales, used in the clinical practice of TRD management, aiming to identify clinical markers predictive of response to Esketamine;
- to evaluate differences in remission rates (MADRS score < 10) in different clinical profiles of patients with TRD.

Materials and methods

This will be an observational, retrospective and multicentric study conducted on a sample of patients with TRD treated with Esketamine nasal spray on the recommendation of a psychiatrist and in compliance with the indications provided by AIFA and the common clinical practice of TRD management.

Several centers will be involved in this study: the coordinating centers will be the "G. d'Annunzio" University of Chieti and the University of Brescia.

Other centers involved will be: Cattolica del Sacro Cuore "A. Gemelli" University Hospital of Rome, "A. Moro" University of Bari, Tor Vergata University of Rome, "Milano Statale" University, "Milano Bicocca" University, University of Siena, "Magna Graecia" University of Catanzaro, University of Pavia, University of Torino, "Villa Maria Pia" Clinic of Rome, "Von Siebenthal" Clinic of Rome, ASL Frosinone, ASL Napoli 1, ASL Sud Tirolo, ASL Messina, ASL Umbria 2.

In this retrospective study, psychometric scales and clinical information will be analyzed in patients with TRD who already performed treatment with Esketamine Nasal Spray.

Clinical and psychopathological parameters related to three different stages will be considered: baseline (T0), 1 month (T1) and three months (T2) from the treatment beginning.

Inclusion Criteria

- Patients over 18 years of age.
- Patients with a Major Depressive Episode, undergoing

at least two conventional antidepressant treatments in the absence of an adequate clinical response (TRD).
- Patients in treatment with an SSRI or SNRI.
- Patients for whom Esketamine nasal spray treatment has been considered appropriate, according to AIFA indications and common clinical practice of TRD management, regardless of the study.

Exclusion Criteria

- Comorbid organic pathologies (untreated arterial hypertension, previous cerebro-vascular disorders) which represent an absolute contraindication to Esketamine according to AIFA.

Anamnestic data

Anamnestic data will be considered concerning aspects related to affective temperament, any previous manic or hypomanic episodes, family history for mood disorders, concomitant use or substance abuse, number of previous depressive episodes, duration of the current depressive episode.

Psychometric scales

The scales considered at times T0, T1 and T2 will be as follows:
- **Montgomery Asberg Depression Rating Scale** (MADRS-10 items): to assess the severity of mood disorders, concentration, physical condition, sleep disorders found in depressive states [27];
- **Brief Psychiatric Rating Scale** (BPRS-24 items): for an assessment of the global psychopathological condiction [28];
- **Hamilton Depression Scale** (HAM-D-21 items): to assess the severity and pervasiveness of depression;
- **Beck Depression Inventory** (BDI-21 items): self-administered scale consisting of 21 items to evaluate the subjective perception of depressive symptoms;
- **Hamilton Anxiety Scale** (HAM-A-21 items): to assess the severity of the anxious symptoms.

Sample size calculation and Statistical Analysis

Sample size was calculated using the G*Power software and the ANOVA: repeated measures, within factors test.
The sample size calculation will be 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. Thus, the estimated sample size will be n = 100.
Statistical analyses will be performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). All tests will be two-tailed, with a statistical significance level set at $p < 0.05$.
Pearson's t-tests for continuous variables and $\chi 2$ tests for categorical variables will be performed. The comparison of psychometric data in the different stages (T0, T1 and T2) will be performed with a t-test for paired samples.
For the identification of predictors of efficacy, change in clinical rating scale scores (response/remission) between the different stages (T0, T1 and T2) will be considered as a dependent variable. Potential predictors (clinical and demographic characteristics, baseline scores and change in clinical measures) will then be included in a multiple regression analysis. Based on clinical and anamnestic data, possible stratification of the sample into different groups will be evaluated, and differences in response and remission between these groups will be assessed through t-test analysis for independent samples.

Ethical considerations

The study will be conducted in accordance with the ethical principles stated in the Helsinki Declaration (2013) [29]. The local ethics committee will examine all documentation to safeguard the rights and confidentiality of the subjects. The protocol and the documentation relating to this study and any revisions of these documents will be used only with the authorization of the local ethics committee.

Discussion

In recent years, new trends in psychiatry have focused on finding innovative and rapidly-acting tools to counteract TRD, considering the global economic and health burden of this disease, with large direct and indirect costs for those affected and their caregivers [30,31].
The rapid onset and the easy way of administration of Esketamine, together with a good safety profile, has determined its recent approval by FDA, EMA and AIFA as therapeutic tool for TRD. Several RCT have shown its antidepressant efficacy when administered together with an oral SSRI/SNRI [23-25], showing a symptoms' remission rate higher than 50% in TRD patients [26].
However, despite the availability of different experimental trial about Esketamine efficacy on TRD, there is a lack of studies conducted in a clinical and non-experimental setting.
In this observational, retrospective and multicentric study, we aim to evaluate the efficacy, safety, and tolerability of Esketamine in a clinical sample of TRD patients from different Italian Mental Health Services. Our goal is to provide a *real-world* experience of Esketamine to better understand its efficacy and safety profile, investigating both mild and serious adverse effects' rates. We will focus on possible risk of manic/hypomanic switches, intensity of dissociative symptoms, evaluating the drop-out rates in a clinical and non-experimental settings. Clinical setting will provide a *real-world* sample, possibly characterized by several differences from the experimental sample of esketamine RCT (with probably higher rates of co-occurrent disorders, substance abuse, longer illness duration and more heterogenous therapies administered).

The secondary aims of our study are in line with the urgent need of "tailored" therapies in the psychiatric field. Clinical markers predictor of response represents an important matter, in particular for TRD, a widespread disease with high economic and social burdens. Considering this, we will investigate any relationship between anamnestic data (e.g. time from disorder onset, episode duration, years of disease, number of episodes, affective temperaments, co-occurrent substance use, comorbidity with other psychiatric disorders) and clinical effectiveness of Esketamine. Besides, possible relationship between type of antidepressant molecules and add-on therapies (SSRI, SNRI, other antidepressants, mood stabilizers, antipsychotics) and clinical efficacy of Esketamine will be assessed.

Predicting esketamine efficacy and create data-driven TRD subtypes based on clinical features would have a significant impact in clinical practice, reducing costs in terms of healthcare expenditure and the average risk of failed trials.

Conclusions

This study will provide a real-world experience of esketamine use in the context of Italian mental health services, highlighting the external validity and clinical practice utility of this novel, rapidly acting tool for TRD. Investigating the use of esketamine in a real-world sample of patients may help to better clarify its clinical efficacy and safety profile, and help clinicians identify patient populations that are more likely to experience positive outcomes following esketamine administration, with significant implications for reducing costs and improving TRD treatments.

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