Study Protocol

Official Title
ESKPSY: Esketamine in Real-World Settings – Clinical Outcomes, Predictors of Response, Life Functioning and Biological Pathways

NCT Number
To be assigned by ClinicalTrials.gov

Date
August 2025

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1. Background and Rationale

Treatment-resistant depression (TRD) represents a significant clinical challenge, with limited effective pharmacological options. Esketamine, a non-competitive NMDA receptor antagonist, has shown promise in improving symptoms in TRD patients, with a rapid onset of antidepressant action. However, not all patients respond equally, and predictors of treatment response remain unclear.

Emerging literature suggests that clinical, biological (including genetic polymorphisms and neuroimaging), and psychosocial variables may contribute to esketamine response variability. Building on studies such as Guglielmo et al. (2023), which explored the role of temperament and cumulative resistance, this study aims to deepen understanding of real-world predictors of esketamine effectiveness and safety.

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2. Study Objectives

Primary Objective:

- To identify predictive factors (clinical, biological, psychophysical, and functional) of clinical response to esketamine in patients with treatment-resistant depression.

Secondary Objectives:

- To evaluate the effectiveness and safety of esketamine in a real-world clinical setting.
- To explore changes in psychosocial and occupational functioning over time.
- To investigate biological pathways associated with treatment response, including genetic polymorphisms (SNPs), neuroimaging data, and psychophysical tasks (e.g., temporal bisection).

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3. Study Design

- **Study Type:** Observational

- **Design:** Prospective, longitudinal, single-arm (case-only)
- **Duration:** From enrollment to 12 months of treatment
- **Setting:** Real-world clinical practice across outpatient psychiatric centers in Italy
- **Estimated Enrollment:** 100

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4. Population

Inclusion Criteria:

- Adults (≥18 years) diagnosed with Major Depressive Disorder (MDD), meeting criteria for treatment-resistant depression (failure of ≥2 antidepressants)
- Eligible for esketamine treatment as per national guidelines
- Ability to provide informed consent

Exclusion Criteria:

- Current diagnosis of psychotic disorder
- Contraindications to esketamine
- Substance use disorder (moderate to severe) in the past 6 months
- Significant cognitive impairment or neurological conditions

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5. Intervention (Observed Treatment)

- **Esketamine nasal spray**, administered in accordance with the approved product label:
  - Dosage ranging from **28 mg to 84 mg per week**
  - **Twice-weekly administration during the first month**, followed by weekly maintenance

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6. Outcome Measures

Primary Outcome:

- Identification of **predictive factors of clinical response** to esketamine, measured using standard clinical scales (e.g., MADRS) at baseline and regular follow-ups.

Secondary Outcomes:

- Changes in depressive symptoms over time
- Changes in social and occupational functioning
- Safety and tolerability (adverse events monitoring)
- Associations between response and:
  - Genetic polymorphisms (SNPs)
  - Neuroimaging features (e.g., structural and functional MRI)
  - Psychophysical performance (e.g., temporal bisection tasks)

7. Data Collection and Timepoints

- **Baseline**: Clinical, demographic, neuroimaging, genetic, psychophysical assessments
- **Follow-ups**: At 1, 3, 6 and 12 months
    - Clinical scales
    - Functional assessments
    - Safety monitoring

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8. Statistical Analysis Plan (SAP)

- **Descriptive statistics** for demographic and clinical variables
- **Logistic regression** and **machine learning models** to identify predictive factors of response
- **Longitudinal analysis (mixed-effects models)** for symptom trajectories and functioning
- Correction for multiple comparisons where appropriate (e.g., false discovery rate)

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9. Ethics and Dissemination

- The study will be conducted in accordance with the Declaration of Helsinki.
- Ethical approval has been or will be obtained from local institutional review boards.
- Results will be submitted for publication in peer-reviewed journals and presented at international psychiatric conferences.

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10. Funding and Conflicts of Interest

- The investigators declare no conflicts of interest unless otherwise stated.