

# Changes in stress hormones in patients with treatment-resistant depression treated with ketamine

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		<input type="checkbox"/> Results
<b>Last Edited</b> 24/09/2025	<b>Condition category</b> Mental and Behavioural Disorders	<input type="checkbox"/> Individual participant data
		<input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Depression is a common and serious illness that can last a long time or keep coming back. Some people have “treatment-resistant depression” (TRD), which means that at least two different antidepressants have not worked for them. This type of depression is especially hard to treat and can lead to more serious problems, like a higher risk of suicide and difficulties in daily life. Ketamine is a newer medicine that can work quickly for some people with TRD. Scientists think that two hormones related to stress — cortisol and aldosterone — might be out of balance in people with depression. This study wants to find out how these hormone levels in saliva change during ketamine treatment, and whether these changes are linked to feeling better.

### Who can participate?

Adults aged 18 to 65 years who have been diagnosed with a depressive episode, including those with treatment-resistant depression, may be able to take part.

### What does the study involve?

Participants will stay in hospital and receive standard ketamine treatment through a drip in the arm, three times a week (for example, Monday, Wednesday, and Friday). The total number of treatments will be between three and six, depending on how well the person responds.

During the study, participants will:

- Have a mental health assessment
- Fill out questionnaires about their symptoms
- Give saliva samples at different times to measure hormone levels (before treatment, after some treatments, at the end, and possibly at a 3-month follow-up)
- Complete depression rating scales at several points during and after treatment
- Some participants may also be asked to do an extra test (a low-dose dexamethasone suppression test) before the first saliva sample, but this is optional.

### What are the possible benefits and risks of participating?

Taking part may help researchers understand more about how ketamine works and how stress hormones are involved in depression. This could help improve treatment in the future.

However, there may be risks or side effects from ketamine, such as feeling strange or dizzy, or other possible side effects discussed with the medical team. Giving saliva samples and filling out questionnaires are low risk.

Where is the study run from?

Department of Psychiatry of Faculty of Medicine, Comenius University and University Hospital Bratislava (Slovakia)

When is the study starting and how long is it expected to run for?

June 2025 to October 2026

Who is funding the study?

Comenius University in Bratislava (Slovakia)

Who is the main contact?

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## Contact information

### Type(s)

Public, Scientific, Principal investigator

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## **Additional identifiers**

### **Clinical Trials Information System (CTIS)**

Nil known

### **Protocol serial number**

Nil known

## **Study information**

### **Scientific Title**

Neuroendocrine correlates of antidepressant response to ketamine in patients with treatment-resistant depression

### **Acronym**

NeCoAnReKe

### **Study objectives**

Main objective: The relationship between salivary aldosterone and cortisol concentrations, their daily release rhythms and mutual ratio, in patients with treatment-resistant depression treated with ketamine.

### **Hypotheses:**

H1: Ketamine treatment leads to a decrease in salivary aldosterone concentration and a change in its diurnal rhythm (i.e. a steeper decline from morning to evening) compared to baseline values, which correlates with the reduction of depressive symptoms.

H2: Patients with higher baseline salivary aldosterone concentrations exhibit a greater antidepressant response to ketamine.

H3: Diurnal cortisol rhythms remain unchanged after ketamine treatment, consistent with cortisol's role as a trait marker.

H4: In patients with depression, cortisol levels remain unsuppressed after administration of dexamethasone, indicating impaired feedback inhibition of the HPA axis.

### **Ethics approval required**

Ethics approval required

### **Ethics approval(s)**

approved 23/06/2025, Ethics Committee of Faculty of Medicine, Comenius University and University Hospital Bratislava (Mickiewiczova 13, Bratislava, 81369, Slovakia; +421 905563757; janpecenak@gmail.com), ref: 15/2025

### **Study design**

Open naturalistic prospective longitudinal observational study

### **Primary study design**

Observational

**Study type(s)**

Treatment

**Health condition(s) or problem(s) studied**

Response to ketamine in patients with treatment-resistant depression

**Interventions**

All participants will receive intravenous ketamine as part of standard clinical treatment for treatment-resistant depression (TRD), administered 3 times per week (e.g., Monday, Wednesday, Friday), for a total of 3 to 6 infusions. The number of infusions will be determined based on clinical response. The study does not alter or randomize the treatment procedure.

As part of the research protocol, participants will provide saliva samples for the measurement of aldosterone and cortisol at defined time points: prior to treatment (morning and evening), after the first infusion, after the third infusion (morning and evening), after the final infusion (morning and evening) and at 3-month follow-up (optional). They will also complete depression rating scales (MADRS, PHQ-9) at baseline, after the third infusion, at the end of ketamine treatment, and at 3-month follow-up.

A subset of participants will optionally undergo a low-dose dexamethasone suppression test before the first saliva collection.

**Intervention Type**

Drug

**Phase**

Not Applicable

**Drug/device/biological/vaccine name(s)**

Ketamine hydrochloride

**Primary outcome(s)**

1. Salivary aldosterone and cortisol concentrations and their diurnal rhythms (morning vs evening levels)
2. Hormone levels will be measured at baseline (before first infusion), after the third infusion, after the final infusion, and at 3-month follow-up.
3. Aldosterone will be measured using a modified radioimmunoassay (RIA) method; cortisol will be measured using a commercial ELISA kit.

**Key secondary outcome(s)**

1. Depressive symptom severity, assessed by the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Patient Health Questionnaire (PHQ-9), measured at baseline, after the third infusion, after the final infusion, and at 3-month follow-up.
2. Salivary cortisol levels and rhythm, measured alongside aldosterone at all time points (baseline, post-third infusion, post-final infusion, and 3-month follow-up), assessed for trait-like stability.
3. Response to the dexamethasone suppression test (DST) in a subset of participants, assessed via salivary cortisol concentrations before and after 1 mg dexamethasone administration.

**Completion date**

01/10/2026

# Eligibility

## Key inclusion criteria

1. Age between 18 and 65 years
2. Diagnosis of a current depressive episode according to ICD-10 criteria, including:
  - F32.x – Depressive episode
  - F33.x – Recurrent depressive disorder
  - F31.x – Bipolar affective disorder, current episode depressive
  - F41.2 – Mixed anxiety and depressive disorder
3. Body Mass Index (BMI) between 18.5 and 28 kg/m<sup>2</sup>
4. Eligible for treatment with intravenous ketamine as part of standard care for treatment-resistant depression
5. Ability and willingness to provide written informed consent

## Participant type(s)

Patient

## Healthy volunteers allowed

No

## Age group

Adult

## Lower age limit

18 years

## Upper age limit

65 years

## Sex

All

## Total final enrolment

40

## Key exclusion criteria

1. History of organic brain damage or cerebrovascular accident
2. Current or past substance abuse or dependence
3. Diagnosed endocrinopathy (except for compensated hypothyroidism)
4. Pregnancy, lactation, or current hormone therapy
5. Presence of psychiatric diagnoses outside of the target ICD-10 categories, including:
  - 5.1. Schizophrenia spectrum and other psychotic disorders (F20–F29)
  - 5.2. Personality disorders (F60–F69)
  - 5.3. Neurodevelopmental disorders
  - 5.4. Any mental disorder not listed in inclusion criteria
6. Current corticosteroid treatment
7. Diagnosed autoimmune disease
8. Use of medications that affect the renin-angiotensin-aldosterone system, including:

- 8.1. ACE inhibitors
- 8.2. Angiotensin II receptor blockers (sartans)
- 8.3. Spironolactone

**Date of first enrolment**

01/10/2025

**Date of final enrolment**

15/09/2026

## **Locations**

**Countries of recruitment**

Slovakia

**Study participating centre**

**Psychiatric Department of the Faculty of Medicine of Comenius University and University Hospital Bratislava**  
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Bratislava  
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## **Sponsor information**

**Organisation**

Department of Psychiatry of Faculty of Medicine, Comenius University and University Hospital Bratislava

## **Funder(s)**

**Funder type**

University/education

**Funder Name**

Univerzita Komenského v Bratislave

**Alternative Name(s)**

Univerzita Komenského, Comenius University in Bratislava, Comenius University

**Funding Body Type**

Government organisation

## **Funding Body Subtype**

Local government

## **Location**

Slovakia

# **Results and Publications**

## **Individual participant data (IPD) sharing plan**

Individual participant data (IPD) will be available upon reasonable request.

De-identified data may be shared with qualified researchers for ethically approved secondary analyses, subject to a data-sharing agreement. Requests will be reviewed by the study team to ensure appropriate use and data protection. No personal identifiers will be included.

## **IPD sharing plan summary**

Available on request