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

Submission date
22/09/2025

Recruitment status
Not yet recruiting

Registration date
25/09/2025

Overall study status
Ongoing

Last Edited
24/09/2025

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] 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

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
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

Secondary study design
Longitudinal study

Study setting(s)
Hospital, Laboratory, University/medical school/dental school

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

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

Pharmaceutical study type(s)
Not Applicable

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Ketamine hydrochloride

Primary outcome measure

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.

Secondary outcome measures
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.

Overall study start date
23/06/2025

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/m²
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

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
Both

Target number of participants
30

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
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Sponsor information

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Sponsor type
Hospital/treatment centre

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

Publication and dissemination plan
Planned publication in a peer-reviewed journal

Intention to publish date
31/12/2027

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