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Serotonin effects on brain function and their relationship to relapse when stopping antidepressants

Submission date	Recruitment status	[ ] Prospectively registered
13/03/2026	Recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
12/05/2026	Ongoing	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
12/05/2026	Mental and Behavioural Disorders	[X] Record updated in last year

Plain English summary of protocol

Background and study aims

Many people experience a relapse of depression if and when they stop their antidepressant medication. We do not know how stopping antidepressants leads to depression returning. We also do not know who will have a relapse if they stop their medication. This study aims to understand this better.

The study will use behavioural and brain measurements (magnetoencephalography; MEG). It will look at the effect of briefly and reversibly lowering serotonin through a dietary manipulation (acute tryptophan depletion; ATD) akin to a protein drink. This is thought to 'simulate' what happens when antidepressants are stopped. Looking at brain function at this time might help us understand how stopping antidepressants results in relapse. The study will work with people who had depression but are now well, while still taking an antidepressant medication, but would like to stop. Participants will undergo brain imaging and ATD before stopping their medication, and will then be monitored for a relapse of depression for six months. This way, the relationship between lowering serotonin in brain function and the relapse after stopping antidepressants can be better understood.

Ultimately, the hope is that the measurements could help us understand what the mechanisms of depression relapse after antidepressant discontinuation are, and how serotonin is involved in it.

Who can participate?

Adults between 18-64 years who had depression, but are now well, who are taking an antidepressant medication and would like to stop their antidepressant medication.

What does the study involve?

- Participants will stop their antidepressant medication
- They will do tasks on the computer at home after they have stopped their antidepressant medication.
- The study team will monitor how participants are doing through regular phone/video calls.

What are the possible benefits and risks of participating?
Benefits: The study team will monitor participants' depression carefully while and after they stop their antidepressant medication. This could allow them to restart treatment quickly if another depressive episode occurs. The results of this study may improve treatment and increase understanding of treatments for future patients.
Risks: Acute tryptophan depletion has a well-characterized safety profile. The main risk is a temporary occurrence or worsening of depressive symptoms, with the possibility of temporary suicidal thoughts occurring. These can be mitigated by providing food containing tryptophan. Other possible side effects include nausea, headache, dizziness, or gastrointestinal discomfort, which can be mitigated by mixing the amino acid drinks with chocolate or strawberry flavour to improve the flavour.

Where is the study run from?
University College London (UK).

When is the study starting and how long is it expected to run for?
April 2026 to February 2029

Who is funding the study?
Wellcome Trust, UK

Who is the main contact?
1. Dr Michaela Poppe (public), m.poppe@ucl.ac.uk
2. Professor Quentin Huys (scientific), q.huys@ucl.ac.uk

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Integrated Research Application System (IRAS)
365238

Central Portfolio Management System (CPMS)
72937

Wellcome Trust grant code
221826/Z/20/Z

Study information

Scientific Title
Predicting Relapse After Discontinuing Antidepressants using acute tryptophan depletion and Magnetoencephalography

Acronym
PRADAM

Study objectives
1. To examine the reversible and temporary impact of reducing serotonin on cognition in people who have recovered on serotonergic antidepressants and are still taking their antidepressant medication
2. To examine whether the cognitive and affective effects of reducing serotonin relate to who will experience a relapse of depressive symptoms when they stop serotonergic antidepressant medications

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 01/04/2026, East Midlands - Leicester South Research Ethics Committee (3 Piccadilly Place, London Road, Manchester, M1 3BN, United Kingdom; +44 207 104 8193; Leicestersouth.rec@hra.nhs.uk), ref: 26/EM/0044

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Blinded (masking used)

Control
Placebo

Assignment
Crossover

Purpose
Basic science, Diagnostic

Study type(s)

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

Interventions
This is a basic science study involving procedures with human participants. Participants in the study will visit UCL for two study days prior to tapering their antidepressant medication. On these days, they will undergo a within-subject, randomized, double-blind, controlled dietary manipulation and brain imaging using magnetoencephalography (MEG). The randomisation element determines who receives the active amino acid mix on Day 1 and who receives it on Day 2. All participants will receive the active amino acid mixture - some will get the active mixture on Day 1 and the control mixture on Day 2, and others will get the active mixture on Day 2 and the control mixture on Day 1. They will also do behavioural tasks and fill in questionnaires. They will then taper their medication down and enter follow-up for 6 months to assess for a relapse of depression.

Study participation will not entail meaningful changes to the participant's depression treatment. However, monitoring after the discontinuation may help re-engage treatment quickly if appropriate.

Antidepressant discontinuation is entirely clinically managed and would occur irrespective of study participation; the research protocol does not prescribe, modify, or evaluate medication dosing. Participants will be free to adjust the tapering speed in consultation with their GP or prescribing doctor.

Randomisation:
Blocked, fully concealed 1:1 randomisation. A randomiser independent from the study team produced the randomisation list and informed the kit producer directly. Kits were labelled with a random alphanumeric keycode.

Intervention Type
Other

Primary outcome(s)
1. Behavioural and neural markers of cognition measured using computational models of behaviour and magnetoencephalography at visit 1 and visit 2

2. Relapse of Major Depressive Disorder measured using structured clinical interview at study exit

Key secondary outcome(s)
1. Depression measured using the Patient Health Questionnaire - 9 (PHQ-9) at Baseline, acute tryptophan depletion (ATD) Day 1, ATD Day 2

2. Depression measured using the Inventory of Depressive Symptomatology (IDS-SR-30) at Baseline, ATD Day 1, ATD Day 2

3. Anxiety Severity measured using the Generalised Anxiety Disorder Questionnaire (GAD-7) at Baseline, ATD Day 1, ATD Day 2

4. Health impairment measured using the Work and Social Adjustment Scale (WSAS) at Baseline, ATD Day 1, ATD Day 2

5. Quality of Life measured using the ICEpop CAPability measure for Adults (ICECAP-A) at Baseline, ATD Day 1, ATD Day 2

6. Personality measured using the Big Five Inventory (BFI-10) at Baseline, ATD Day 1, ATD Day 2

7. Reward functioning measured using the Positive Valence Systems Scale (PVSS) at Baseline, ATD Day 1, ATD Day 2

8. Activation/engagement measured using the Behavioral Activation for Depression Scale – Short Form (BADS-SF) BADS-SF at Baseline, ATD Day 1, ATD Day 2

9. Hopelessness measured using the Brief Hopelessness scale at Baseline, ATD Day 1, ATD Day 2

10. Rumination measured using the Ruminative Response Scale, brooding subscale at Baseline, ATD Day 1, ATD Day 2

11. Negative emotion responses measured using the PERS negative activation subscale at Baseline, ATD Day 1, ATD Day 2

12. Blood plasma ratio of tryptophan to large neutral amino acids measured using (TRP/LNAA ratio) at ATD Day 1, ATD Day 2

Completion date
01/02/2029

Eligibility

Key inclusion criteria
1. Have had at least two episodes of depression
2. Be aged 18 to 64 (older people are excluded as different assessments for depression are used in older age groups)
3. Be taking a serotonergic antidepressant medication (citalopram 20 mg or more, escitalopram 10 mg or more, sertraline 100 mg or more, fluoxetine 20 mg or more, paroxetine 20 mg or more, clomipramine 50 mg or more or mirtazapine 15 mg or more) that was started to treat an episode of depression
4. Be in stable remission for the past 6 weeks, with a Patient Health Questionnaire (PHQ-9) total score less than 7
5. Have satisfactory treatment adherence to medication
6. Be intent on stopping their antidepressant medication

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit

64 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Meet internationally agreed (ICD-10) criteria for a depressive illness
2. Have a baseline PHQ-9 score greater than or equal to 10
3. Have bipolar disorder, psychotic illness, dementia, alcohol or substance use disorder or a terminal illness
4. Are not able to complete self-administered questionnaires in English
5. Are pregnant or intend to get pregnant within the next 6 months
6. Fail the pre-test online behavioural task assessment
7. Meet any MEG exclusion criteria including:
7.1. Epilepsy
7.2. Insulin-dependent diabetes
7.3. Magnetic parts in the upper body or head (such as piercings, dental wire, permanent eye-liner)
7.4. Are otherwise not able to tolerate or not suitable for MEG

Date of first enrolment
13/04/2026

Date of final enrolment
12/04/2028

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University College London Division of Psychiatry and Queen Square Institute of Neurology
10-12 Russell Square
London
England
WC1E 5BH

Sponsor information

Organisation

University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publicly available repository. Further details are not yet available.

IPD sharing plan summary
Stored in publicly available repository