ISRCTN77976141 https://doi.org/10.1186/ISRCTN77976141

Reinforcement learning mechanisms of pharmacological treatments for depression

Submission date
04/12/2024

Recruitment status
Recruiting

Registration date
16/12/2024

Overall study status
Ongoing

Last Edited
26/10/2026

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 an important disorder. Although many different antidepressant drugs exist, no tests to tell us which antidepressant is most likely to work for any one individual. As a result, treatments are often trial-and-error: people often have to try several antidepressant drugs before they find one that works for them. This study is part of a 2-study funded research programme. It will aim to develop tests that may be able to tell us in advance who will respond to which drug. UK primary care patients with depression will be given one of two antidepressants, escitalopram or bupropion, or a placebo. This study will use tasks on the computer and brain recordings to measure their “reinforcement learning”. Reinforcement learning depends on the same brain chemistry that antidepressants act on. Importantly, different components of reinforcement learning depend on different aspects of brain chemistry, and may hence be able to tell apart how different antidepressants work. The first trial (RELMED-I, the current study) will examine broad components of reinforcement learning. The second study (RELMED-II, a future study) will then build on the first study and test specific components. If different components of reinforcement learning are sensitive to different antidepressants, this can be used to build tests to identify who is likely to benefit most from which treatment.

Who can participate?
People aged 18 years old or above who have depression and are under the care of a participating GP in the UK can take part.

What does the study involve?
Eligible participants will be randomised to 1) Bupropion, 2) Escitalopram, 3) placebo followed by bupropion after 2 weeks or 4) placebo followed by escitalopram after 2 weeks. Blinded trial medication is taken for 8 weeks at which point it will be offered open-label to participants until Week 26. Participants will be asked to complete computer-based reinforcement learning tasks and questionnaires at baseline and follow-up. Participants will be followed up for 52 weeks. Participants are also invited to take part in two optional EEG assessments.

What are the possible benefits and risks of participating?
Benefits: Participants have a 50% chance of being treated with bupropion, which is usually only prescribed by specialists. The antidepressant treatment may help to treat participants’

depression but this cannot be guaranteed. However, the results of this trial may improve treatment and increase understanding of treatments for future patients.

Risks: Escitalopram and Bupropion can cause side effects. People taking higher doses are more likely to feel side effects. Both medications can have serious side effects if someone suffers from certain illnesses, or if they are taken in combination with certain other medications. Participants' medical history and current medications will be checked as part of the eligibility screening. The dose can be reduced or participants can withdraw if side effects occur. Escitalopram and Bupropion may harm unborn babies and may be passed through breast milk. Therefore, women who are pregnant, breastfeeding, or planning pregnancy and who do not wish to use effective contraception cannot take part in the trial.

Where is the study run from?
University College London. Additional sites include Oxford, Nottingham, Bristol and Newcastle.

When is the study starting and how long is it expected to run for?
March 2024 to June 2027

Who is funding the study?
Wellcome Trust, UK

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

Contact information

Type(s)
Principal investigator

Contact name
Prof Quentin Huys

ORCID ID
https://orcid.org/0000-0002-8999-574X

Contact details
Queen Square Institute of Neurology
10-12 Russell Square
London
United Kingdom
WC1E 5BH
-
q.huys@ucl.ac.uk

Type(s)
Public, Scientific

Contact name
Dr Michaela Poppe

Contact details
UCL Division of Psychiatry
4th Floor Maple House
149 Tottenham Court Road
London
United Kingdom
W1T 7NF
+44 (0)20 7679 9311
m.poppe@ucl.ac.uk

Additional identifiers

Integrated Research Application System (IRAS)
345935

Central Portfolio Management System (CPMS)
64366

Protocol serial number
Wellcome Trust grant code: 226790/Z/22/Z

Study information

Scientific Title
Reinforcement learning mechanisms of pharmacological treatments for depression: a double-blind, four-arm, placebo-controlled multi-site trial in UK primary care. Trial 1.

Acronym
RELMED-I

Study objectives
The study objectives are the following:
Test whether serotonergic and catecholaminergic antidepressants alter different, specific, reinforcement learning (RL) processes.
Primary objective: Test the RL parameters at week 2, comparing:
A) Escitalopram and Placebo
B) Bupropion and Placebo
C) Bupropion and Escitalopram
Secondary objectives include RL behaviour parameters at week 4, EEG parameters at week 2 and week 4 and correlations with self-reported symptoms.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 07/01/2025, South Central - Berkshire Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8178; berkshire.rec@hra.nhs.uk), ref: 24/SC/0411

Primary study design

Interventional

Study design
Randomized double-blind placebo-controlled clinical trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Reinforcement-learning processes engaged by two established antidepressant treatments

Interventions
This trial examines the reinforcement-learning processes engaged by two established antidepressant treatments, escitalopram and bupropion, to improve treatment in the future. This is a mechanistic study of the investigational treatments, with differences in the neurocognitive mechanisms as primary endpoints. The safety and efficacy of both investigational treatments have been extensively established previously. Hence, this trial is not a Clinical Trial of an Investigational Product (CTIMP).

Participants will be randomised using a web-based randomisation system provided by Sealed Envelope with a 2:2:1:1 ratio to receive either:
- 8 weeks escitalopram
- 8 weeks bupropion
- 2 weeks placebo followed by 6 weeks escitalopram
- 2 weeks placebo followed by 6 weeks bupropion.

After 8 weeks, all participants will be offered open-label continuation of the medication for a full treatment course, up to 26 weeks in total to ensure that those who respond to the treatment can receive a full course and do not have to discontinue an effective treatment earlier than recommended by guidelines. Participants will be tapered off medication at the end of the open-label phase and followed up to monitor for relapse for up to one year (unless there is an agreement with the GP that the medication prescription will be taken over by the GP and continued).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Escitalopram, bupropion

Primary outcome(s)
Reinforcement learning mechanism measured using a computer-based behavioural task at baseline, weeks 2 and 4 and optionally at weeks 24 and 28

Key secondary outcome(s)
1. Depression measured using the Patient Health Questionnaire - 9 (PHQ-9) at Screening, Baseline, Week 2, 4, 6, 8, 24, 28 and 52
2. Health impairment measured using the Work and Social Adjustment Scale (WSAS) at

Screening, Week 6, 8, 24, 52
3. Quality of Life measured using the ICEpop CAPability measure for Adults (ICECAP-A) at Screening, Week 6, 8, 24 and 52
4. Personality measured using the Big Five Inventory (BFI-10) at Screening
5. Anxiety Severity measured using the Generalised Anxiety Disorder Questionnaire (GAD-7) at Baseline, Week 2, 4, 6, 8, 24, 28 and 52
6. Reward functioning measured using the Positive Valence Systems Scale (PVSS) at Baseline, Week 2, 4, 6, 8, 24, 28 and 52
7. Activation/engagement measured using the Behavioral Activation for Depression Scale – Short Form (BADS-SF) BADS-SF at Baseline, Week 2, 4, 6, 8, 24, 28 and 52
8. Hopelessness measured using the Brief Hopelessness scale at Baseline, Week 2, 4, 6, 8, 24, 28 and 52
9. Rumination measured using the Ruminative Response Scale, brooding subscale at Baseline, Week 2, 4, 6, 8, 24, 28 and 52
10. Negative emotion responses measured using the PERS negative activation subscale at Baseline, Week 2, 4, 6, 8, 24, 28 and 52
11. EEG parameters measured using optional EEG assessments at Baseline and Week 2

Completion date
30/06/2027

Eligibility

Key inclusion criteria
1. Meeting diagnostic criteria for a DSM-5 Major Depressive Episode on the affective disorder sections of the Mini International Neuropsychiatric Interview (MINI)
2. Patient Health Questionnaire (PHQ-9) total score > = 10
3. Under the care of a GP in the UK
4. Aged 18 years and above
5. Able to provide informed consent to participate in the trial
6. Women of childbearing potential (WOCBP) must be willing to use an effective method of contraception (hormonal or barrier method of birth control; true abstinence) from the time consent is signed until six weeks after treatment discontinuation and inform the trial if pregnancy occurs. For clarity, true abstinence is when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence, withdrawal, spermicides only or lactational amenorrhoea method for the duration of a trial, are not acceptable methods of contraception
7. Women of Child Bearing Potential (WOCBP) must have a negative urine pregnancy test before randomisation.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Contraindications to treatment with bupropion: acute alcohol withdrawal; acute benzodiazepine withdrawal; history of mania; CNS tumour; current or past eating disorders; history of seizures; severe hepatic cirrhosis; concomitant use of monoamine oxidase inhibitors (MAOIs)
2. Contraindications to treatment with escitalopram: history of seizures; history of mania; QT-interval prolongation; known difficulty to control hypertension; active cardiac disease
3. Known hypersensitivity or allergies to escitalopram, bupropion or their excipients
4. Pharmacological treatment for depression in the past 6 weeks
5. Current medication for depression (e.g. with a mood stabiliser, antipsychotic or antidepressant), or any other dopaminergic, noradrenergic or serotonergic medication
6. Significant neurological impairment
7. Significant active suicidality
8. Current clinically significant substance use disorder
9. Clinically significant medical conditions under investigation or acute treatment
10. Pregnant, breastfeeding or planning pregnancy
11. Incomplete first online behavioural assessment & call

Date of first enrolment
28/05/2025

Date of final enrolment
30/04/2027

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

Study participating centre
Warneford Hospital
Department of Psychiatry
Warneford Lane
Headington
Oxford
England
OX3 7JX

Study participating centre
University of Nottingham
Institute of Mental Health
Jubilee Campus, Wollaton Road
Nottingham
England
NG8 1BB

Study participating centre
University of Bristol
Bristol Medical School
Oakfield House, Oakfield Grove,
Clifton
Bristol
England
BS8 2BN

Study participating centre
Newcastle University
Academic Psychiatry and Regional Affective Disorders Service
Wolfson Research Centre, Campus for Ageing and Vitality
Newcastle upon Tyne
England
NE4 5PL

Sponsor information

Organisation
University College London

ROR

https://ror.org/02jx3x895

Funder(s)

Funder type
Government

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