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Is pramipexole effective as an add-on treatment for people with treatment-resistant depression?

Submission date
26/02/2019

Recruitment status
No longer recruiting

Registration date
15/05/2019

Overall study status
Completed

Last Edited
03/07/2025

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
Clinical depression is a common disorder usually treated in primary care with psychological therapies and antidepressant medication. However a significant proportion of people (about 2-3 in 10) do not improve with current first-line therapies and are regarded as having treatment resistant depression (TRD).
TRD is a major problem for both patients and society because of the high level of suffering and associated disability. Current medicines for TRD are not particularly effective for many people and often have adverse effects which patients find distressing.
There is some evidence that pramipexole, a medicine already commonly used in Parkinson's Disease, may be an effective treatment for TRD. PAX-D will compare the effects of pramipexole with placebo when added to current antidepressant medication for people with TRD. The trial will look at effectiveness in the short- term (after 12 week's treatment) and in the longer-term (48 weeks). The trial will also assess the adverse effects of pramipexole and explore patients' experiences of taking it.
Pramipexole is unlike current antidepressant drugs in that it acts like a brain chemical called dopamine, which is known to influence people's motivation to pursue goals and affect how rewarding they find them. Lack of motivation is a key symptom of depression so any antidepressant effects of pramipexole may be linked to increased motivation. PAX-D participants will be asked to carry out a computer task designed to measure how pramipexole affects the dopamine system in the brain and how far this can explain its antidepressant effects.
If pramipexole is effective it could become a very useful treatment option for patients with TRD and this information will be disseminated through scientific publications, meetings with patient groups and NHS innovation programmes.

Who can participate?
People aged over 18 years old with a diagnosis of Treatment Resistant Depression.

What does the study involve?
Participants will attend a screening visit to confirm that they are eligible to join the trial. They will then be randomly assigned to receive either pramipexole or to a placebo and will attend a further four study visits over 48 weeks. At study visits, participants will be asked to complete questionnaires and will complete a cognitive task at a computer. Between study visits,

participants will be contacted by a trained research assistant and asked to regularly complete questionnaires by phone and by using an online system called True Colours.

What are the possible benefits and risks of participating?
The aim of the trial is to find out if pramipexole is a useful treatment for treatment resistant depression. If participants are randomised to receive pramipexole, this may help treat their depression but this cannot be guaranteed. Participants using True Colours will be able to monitor their responses to the questionnaires over time and this may provide greater insight into their depression. Pramipexole has a range of common and uncommon side effects. Not everyone will experience side effects to pramipexole but participants will be advised how to recognise them and when to seek medical help. The effects of pramipexole on pregnancy and breast-feeding are not known. Pregnant women will not be able to take part in the trial, and women of childbearing potential will be asked to use effective contraception during the 48-week treatment period.

Where is the study run from?
Warneford Hospital, Oxford, UK

When is the study starting and how long is it expected to run for?
August 2019 to September 2024

Who is funding the study?
NIHR Efficacy and Mechanism Evaluation Programme, UK

Who is the main contact?
1. Mr Alex Lewis (public contact), oxfordhealth.paxd@nhs.net
2. Dr Michael Browning (scientific contact), michael.browning@psych.ox.ac.uk

Contact information

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Public

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Clinical Trials Information System (CTIS)
2019-001023-13

Integrated Research Application System (IRAS)
253702

Protocol serial number
Ox_Psych_PAXD, IRAS 253702

Study information

Scientific Title
Randomised placebo-controlled trial evaluating the efficacy and mechanism of pramipexole as add-on treatment for people with treatment resistant depression

Acronym
PAX-D

Study objectives
That pramipexole will produce greater improvement than placebo in depressive symptoms after twelve weeks of treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/02/2020, South West - Central Bristol Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8061; nrescommittee.southwest-bristol@nhs.net), ref: 19/SW/0216

Study design
Randomised double-blind placebo-controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Treatment resistant depression

Interventions
In addition to their standard antidepressant medication, participants will be randomised 1:1 to receive either Pramipexole dihydrochloride monohydrate or a matched placebo. Randomisation will be via minimisation facilitated by an online randomisation system hosted by the Primary Care CTU at the University of Oxford.

Pramipexole dihydrochloride monohydrate or matched placebo will be initiated at 0.25mg/day and, in the absence of concerns about tolerability, the dose will be increased by 0.25mg/day every three days towards a target dose of 2.5mg/day. Participants unable to tolerate a scheduled dose increase will be advised to remain on the highest tolerable dose.

Participants will be asked to complete the QIDS-SR16 at baseline and at 12 weeks post-randomisation and the scores will be compared between those treated with pramipexole and those treated with placebo. To further understand the mechanism and effects of pramipexole, participants will also complete additional questionnaires and a cognitive task at intervals throughout the 48-week treatment period.

Intervention Type
Drug

Phase
Phase IV

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

Primary outcome(s)
Improvement (change from baseline) of depressive symptoms measured on the Quick Inventory of Depressive Symptomatology, self-report version (QIDS-SR16) measured at baseline and 12 weeks post-randomisation

Key secondary outcome(s))
1. Safety (emergence of new symptoms) and Tolerability during the 48 week randomised phase assessed by:
1.1 Termination of trial treatment due to intolerance
1.2 Adverse reactions
1.3 TSQM
1.4 ALTMAN (manic symptoms)
1.5 QUIP-RS (impulse control)
1.6 Suicidal ideation (QIDS-SR16)
2. Change in reward sensitivity parameter from model fitted to learning/decision making task between baseline, week 2 and 12 weeks
3. Change in QIDS-SR16 and SHAPS scores between baseline and week 12 and change in reward sensitivity between baseline and week 2

4. Change scores in the learning/decision making task at 2 weeks and the change in the QID-SR16 at 12 weeks
5. Baseline scores on the learning/decision making task and the change in QIDS-SR16 at 12 weeks
6. Baseline scores on the SHAPS and change in the QID-SR16 at 12 weeks
7. QIDS-SR16 scores collected weekly across 48 weeks of the trial
8. QIDS-SR16 response, defined as a reduction of ≥50% in baseline score by week 12. QIDS-SR16 remission defined as a score of ≤5 at week 12
9. Change scores for the SHAPS, GAD-7 and QIDS-C between baseline and week 12
10. Change scores for the WSAS-screener between baseline and week 48
11. Change in: EQ-5D-5L, ICECAP-A, and OxCAP-MH over 48 weeks
12. HEQ information and costs over 50 weeks (2 weeks prior to randomisation and 48 weeks during the randomised phase)
13. Qualitative interviews with selected participants and investigators

Completion date
30/09/2024

Eligibility

Key inclusion criteria
Once informed consent has been given, participants will enter a run-in phase prior to randomisation.
Inclusion criteria for entry to run-in phase:
1. Willing and able to give informed consent to participate in the trial
2. Age 18 years or over
3. Diagnosis of DSM-V major depression
4. Quick Inventory of Depressive Symptomatology self-report version (QIDS-SR16) score >10 (moderate, severe or very severe depression)
5. Currently taking and tolerating antidepressant medication
6. Lack of response to at least 2 antidepressants at therapeutic doses (based on Maudsley Prescribing Guidelines and/or British National Formulary) in the current episode
7. Indication for change in treatment
8. Willing to continue an antidepressant treatment
9. Negative urine pregnancy test result (in females of child-bearing potential only)

Inclusion criteria for entry to randomised phase:
1. Verbal consent to randomisation
2. QIDS-SR16 score >10
3. On a stable dose of an antidepressant for at least 4 weeks

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Exclusion criteria for entry to run-in phase:
1. Diagnosis of current or previous psychosis, bipolar disorder or Parkinson's Disease
2. Current antipsychotic medication
3. Clinically significant current or previous impulse control difficulties
4. Serious suicide or homicide risk
5. Current treatment with any medication known to interfere with pramipexole metabolism including cimetidine, memantine and methyldopa
6. Contraindications to pramipexole including history of or current treatment for eye disease, significant, symptomatic cardiovascular or renal disease or significant, symptomatic orthostatic hypotension
7. Previous course of pramipexole (>2 weeks duration)
8. Untreated or unstable medical condition which, in the judgement of the investigator, could interfere with the safety of receiving pramipexole or ability to complete the trial
9. Female and pregnant, lactating or planning pregnancy
10. Female of child-bearing potential not willing to use effective contraception

Exclusion criteria for entry to randomised phase:
1. eGFR (from screening blood test) < 50 mL/min/1.73m2
2. Psychotherapy started in past 4 weeks or planned to start within next 12 weeks

Date of first enrolment
17/08/2020

Date of final enrolment
31/05/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Warneford Hospital
Warneford Lane
Oxford
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
Efficacy and Mechanism Evaluation Programme

Alternative Name(s)
NIHR Efficacy and Mechanism Evaluation Programme, Efficacy and Mechanism Evaluation (EME), EME

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during the current study will be available upon request from Michael Browning (michael.browning@psych.ox.ac.uk). Deidentified individual level data (including DNA samples) will be made available for ethically approved data synthesis and meta-analysis upon receipt of an application and subject to approval by the data sharing committee. Consent for sharing of samples was collected from participants

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		27/06/2025	03/07/2025	Yes	No
HRA research summary			26/07/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes

Study website	Study website	11/11/2025	11/11/2025	No	Yes