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Pramipexole trial for bipolar depression

Submission date	Recruitment status	[X] Prospectively registered
19/08/2019	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
28/08/2019	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
05/06/2025	Mental and Behavioural Disorders	

Plain English summary of protocol

Background and study aims
The aim of this study is to find out whether pramipexole, co-prescribed with a mood stabiliser (lithium, valproate, carbamazepine and/or lamotrigine), is an efficient treatment for treatment-resistant bipolar depression.

Who can participate?
Patients aged 18 years or over with treatment-resistant bipolar depression

What does the study involve?
If participants are on an antipsychotic it is gradually withdrawn, as it may block the effect of pramipexole. Additionally, if participants are not on a 'mood stabiliser', one is started. Once this is done, participants are randomly allocated to receive either pramipexole or placebo (dummy drug), in addition to an ongoing mood stabiliser. The trial team, participants and their treating mental health team do not know whether the participant receives pramipexole or placebo. The effectiveness of pramipexole after 12 weeks is assessed, and participants continue to be monitored by trial researchers for 48 weeks, even if they discontinue the initial treatment, giving real-life information on the use of this treatment. The effect on depressive symptoms and quality of life are assessed, along with side-effects and whether any other treatments are needed. Assessments are self-reported using an online system completed by participants, who are supported by email prompts. These methods have worked well in previous studies and participants approve of their use. The system allows more frequent (weekly) self-ratings of bipolar depression symptoms and thus gives a more complete picture of long-term symptom control. Paper versions are provided where necessary. Participants are telephoned monthly to assess other medication use and side effects.

What are the possible benefits and risks of participating?
Possible risks include adverse effects of pramipexole and/or carbamazepine, lamotrigine, lithium and/or valproate, distress from stopping their usual medication and/or starting a new medication, intrusion and/or inconvenience and/or change to lifestyle of completing online or paper questionnaires, weekly, and taking part in telephone calls with Research Assistants (RAs) and home visits by Clinical Studies Officers or similar. The mitigations to these risks include increased monitoring of the participants than would normally be conducted as part of standard care, including additional support from a wider team (local research team, clinical treating team if separate and RAs). For the participants' convenience and to reduce burden, the study visits can

be conducted in the clinic or in their own home, based on their preference. The eligibility criteria for the trial have been carefully considered to ensure that patients that are suitable to take part can be identified. Additionally, safety will be closely monitored and all participants will be given a safety card to keep on them at all times. This card will include details of the CNTW (Sponsor) out of hours service, which will be available for emergency clinical queries. Participants will also be provided with a participant diary, which will used as an aid to the participant to ensure that they take their medication correctly according to the schedule. Participants will also receive a personalised medication schedule with each prescription, to help with the changes to the medication dose across different periods of the study. The medication labels have been designed so that they are different colours for the two different strengths of tablets, which are also different shapes. This has been incorporated in the patient diary with colour coding and pictures.

Where is the study run from?
Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
September 2019 to March 2023

Who is funding the study?
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC) (UK)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
2018-002869-18

Integrated Research Application System (IRAS)
239794

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
39561, IRAS 239794

Study information

Scientific Title
A randomised, double-blind, placebo-controlled trial of pramipexole in addition to mood stabilisers for patients with treatment-resistant bipolar depression

Acronym
PAX-BD

Study objectives
The PAX-BD trial is a multi-centre, randomised, controlled trial of pramipexole versus placebo, and will elicit whether pramipexole, co-prescribed with a mood stabiliser (lithium, valproate, carbamazepine and/or lamotrigine), is an efficient treatment for treatment-resistant bipolar depression.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 04/09/2019, North East - Newcastle & North Tyneside 2 Research Ethics Committee (NHS BT Blood Donor Centre, Holland Drive, Newcastle upon Tyne, Tyne and Wear, NE2 4NQ, UK; Tel: +44 (0)207 1048091; Email: nrescommittee.northeast-newcastleandnorthtyneside2@nhs.net), REC ref: 19/NE/0233

Study design
Randomized; Both; Design type: Treatment, Drug, Health Economic

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
Current interventions as of 29/07/2022:

The pre-randomisation phase will allow patients to have their antipsychotics adjusted and mood stabiliser initiated if necessary. Once this is done, 290 participants will be randomly allocated in a 1:1 ratio to receive either pramipexole or placebo, in addition to an ongoing mood stabiliser. Randomisations will be carried out by a delegated and trained member of the research team at each site using the Sealed Envelope system (a central, secure, 24-hour web-based randomisation system with concealed allocation). The trial team, participants and their treating mental health team will not know whether the participant receives pramipexole or placebo; the trial is ‘double-blind’.

For all participants, initiation of trial treatment will follow a 4-week titration schedule starting at 0.25 mg/day in a single (oral) dose usually at night for 3 days. Thereafter the dose will be increased by 0.25 mg/day every 3 days. The target dose will be 2.5 mg/day but titration will be based on tolerability and response.

The dose attained at the end of Week 4 is then continued throughout weeks 5-12.

Then from weeks 13- 48 pramipexole will be flexibly dosed between 0.25 and 2.5mg/day, determined by response and tolerability. During the flexible dosing stage of the study, decisions around medication dose alterations will be based on weekly mood scores (QIDS-SR and ASRM) and scores from the side effect items of the TSQM administered 4-weekly. Patient's mood and response and tolerability will be categorised every 4 weeks.

Participants will be provided with medication via 7 separate dispensing at specified timepoints during the study – as part of the last dispensing participants will be provided with enough medication to last them up until week 52 to ensure they have enough to taper down slowly (if this is required) as pramipexole should not be stopped suddenly

The effectiveness of pramipexole after 12 weeks will be assessed, and participants will continue to be monitored by trial researchers for 48 weeks, even if they discontinue the initial treatment, giving real-life information on the use of this treatment. The effect on depressive symptoms and quality of life will be assessed, along with side-effects and whether any other treatments are needed. Assessments will be self-reported using an online system completed by participants, who will be supported by email prompts. These methods have worked well in previous studies and participants approve of their use. The system allows more frequent (weekly) self-ratings of bipolar depression symptoms and thus gives a more complete picture of long-term symptom control. Where necessary paper versions will be provided. Participants will be telephoned monthly to assess concomitant medication use and side-effects.

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Previous interventions:

In the pre-randomisation stage, if participants are on an antipsychotic it will be gradually withdrawn, as it may block the effect of pramipexole. Additionally, if participants are not on a 'mood stabiliser', one will be started. Once this is done, 290 participants will be randomly allocated in a 1:1 ratio to receive either pramipexole or placebo, in addition to an ongoing mood stabiliser. Randomisations will be carried out by a delegated and trained member of the research team at each site using the Sealed Envelope system (a central, secure, 24-hour web-based randomisation system with concealed allocation). The trial team, participants and their treating mental health team will not know whether the participant receives pramipexole or placebo; the trial is 'double-blind'.

For all participants, initiation of trial treatment will follow a 4-week titration schedule starting at 0.25 mg/day in a single (oral) dose usually at night for 3 days. Thereafter the dose will be increased by 0.25 mg/day every 3 days. The target dose will be 2.5 mg/day but titration will be based on tolerability and response.

The dose attained at the end of Week 4 is then continued throughout weeks 5-12.

Then from weeks 13- 48 pramipexole will be flexibly dosed between 0.25 and 2.5mg/day, determined by response and tolerability. During the flexible dosing stage of the study, decisions around medication dose alterations will be based on weekly mood scores (QIDS-SR and ASRM) and scores from the side effect items of the TSQM administered 4-weekly. Patient's mood and response and tolerability will be categorised every 4 weeks.

Participants will be provided with medication via 7 separate dispensing at specified timepoints during the study – as part of the last dispensing participants will be provided with enough medication to last them up until week 52 to ensure they have enough to taper down slowly (if this is required) as pramipexole should not be stopped suddenly

The effectiveness of pramipexole after 12 weeks will be assessed, and participants will continue to be monitored by trial researchers for 48 weeks, even if they discontinue the initial treatment, giving real-life information on the use of this treatment. The effect on depressive symptoms and quality of life will be assessed, along with side-effects and whether any other treatments are needed. Assessments will be self-reported using an online system completed by participants, who will be supported by email prompts. These methods have worked well in previous studies and participants approve of their use. The system allows more frequent (weekly) self-ratings of bipolar depression symptoms and thus gives a more complete picture of long-term symptom control. Where necessary paper versions will be provided. Participants will be telephoned monthly to assess concomitant medication use and side-effects.

Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome(s)
Depression symptoms measured using QIDS-SR questionnaire (Quick Inventory of Depressive Symptomatology) at 12 weeks

Key secondary outcome(s))
Current secondary outcome measures as of 12/10/2020:
1. Mood and anxiety symptoms over 48 weeks, and pleasure symptoms over 12 weeks, measured using the QIDS-SR questionnaire weekly to week 48, the Generalised Anxiety Disorder 7 (GAD-7) weekly to week 48 and the Snaith Hamilton Pleasure Scale (SHAPS) at weeks 0, 6 and 12
2. Psychosocial function measured using the Work and Social Adjustment Scale (WSAS) at weeks 0, 6, 12, 24, 36 and 48
3. Tolerability of pramipexole assessed using rates of AEs, SAEs and SUSARs reported describing severity, seriousness, causality and expectedness
4. Risk of switching to mania and occurrence of psychosis or impulse control disorders, which are known possible side-effects of pramipexole, measured using the Altman Self Rating Scale of Mania (ASRM) questionnaire completed weekly to week 48
5. Rates of impulsivity during treatment with pramipexole, measured using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS) at weeks 0, 6, 12 and then 4-weekly to week 48 (weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48)
6. Side effects and overall acceptability of pramipexole treatment measured using the Treatment Satisfaction Questionnaire for Medication (TSQM) at Weeks 6, 12 and then 4-weekly to week 48 (weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48) and collection of Adverse Events - reported weekly to week 12 and then 4-weekly to week 48 (weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48)
7. Adherence to medication to which patients are randomised via participant reported dose taken during RA phone calls and from central trial medication accountability and reconciliation

records
8. Quality of life assessed using EuroQoL 5 Dimension 5 Level (EQ-5D-5L) at start of pre-randomisation and weeks 0, 6, 12, 24, 36 and 48
9. Capability assessed using the ICEpop CAPability measure for Adults (ICECAP-A) at start of pre-randomisation and weeks 0, 6, 12, 24, 36 and 48
10. Capability in people with mental health problems assessed using the Oxford CAPabilities questionnaire-Mental Health (OxCAP-MH) at start of pre-randomisation and weeks 0, 6, 12, 24, 36 and 48
11. Societal cost assessed uising the Health Economics Questionnaire (HEQ) at start of pre-randomisation and weeks 0, 6, 12, 24, 36 and 48
12. Mania and depression assessed using Young Mania Self-Rating Scale (YMRS) at weeks 0 and 12, Montgomery Asberg Depression Rating Scale (MADRS) at weeks 0 and 12 and Quick Inventory of Depressive Symptomatology – Clinician Rated (QIDS-C) at weeks 0 and 12

Previous secondary outcome measures:
1. Mood and anxiety symptoms over 48 weeks, and pleasure symptoms over 12 weeks, measured using the QIDS-SR questionnaire weekly to week 48, the Generalised Anxiety Disorder 7 (GAD-7) weekly to week 48 and the Snaith Hamilton Pleasure Scale (SHAPS) at week 0, 6 and 12
2. Psychosocial function measured using the Work and Social Adjustment Scale (WSAS) at weeks 0, 6, 12, 24, 36 and 48
3. Cardiovascular side effects of pramipexole via pulse and blood pressure measurements taken at weeks 0, 2, 6, 12, 24, 36 and 48
4. Risk of switching to mania and occurrence of psychosis or impulse control disorders, which are known possible side-effects of pramipexole, measured using the Altman Self Rating Scale of Mania (ASRM) questionnaire completed weekly to week 48
5. Rates of impulsivity during treatment with pramipexole, measured using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS) at weeks 0, 6, 12 and then 4 weekly to week 48 (weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48)
6. Side effects and overall acceptability of pramipexole treatment measured using the Treatment Satisfaction Questionnaire for Medication (TSQM) at Weeks 6, 12 and then 4 weekly to week 48 (weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48) and collection of Adverse Events - reported weekly to week 12 and then 4 weekly to week 48 (weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48
7. Adherence to medication to which patients are randomised via participant reported dose taken during RA phone calls and from central trial medication accountability and reconciliation records
8. Quality of life, wellbeing, health and social care and broader societal costs of patients randomised to either pramipexole or placebo. The incremental cost-effectiveness of pramipexole in comparison to placebo over 48 weeks measured using EuroQoL 5 Dimension 5 Level (EQ-5D-5L) at start of pre-randomisation and weeks 0, 6, 12, 24, 36 and 48, ICEpop CAPability measure for Adults (ICECAP-A) at start of pre-randomisation and weeks 0, 6, 12, 24, 36 and 48, Oxford CAPabilities questionnaire-Mental Health (OxCAP-MH) at start of pre-randomisation and weeks 0, 6, 12, 24, 36 and 48 and the Health Economics Questionnaire (HEQ) at start of pre-randomisation and weeks 0, 6, 12, 24, 36 and 48
9. Mania and depression assessed using Young Mania Self-Rating Scale (YMRS) at weeks 0 and 12, Montgomery Asberg Depression Rating Scale (MADRS) at weeks 0 and 12 and Quick Inventory of Depressive Symptomatology – Clinician Rated (QIDS-C) at weeks 0 and 12

Completion date
01/03/2023

Eligibility

Key inclusion criteria

Current inclusion criteria as of 29/07/2022:

Stage 1/ pre-randomisation:
1. Currently under the care of secondary care mental health services at screening with a plan for the patient to remain in secondary care throughout the period of the trial
2. A decision made by the patient's clinical team that a change in medication is indicated
3. A current diagnosis of Bipolar Disorder (type I or II), defined as in DSM-5, which is supported by the use of the Mini-International Neuropsychiatric Interview (MINI)
4. Currently depressed, i.e. meeting DSM-5 criteria for a Major Depressive Episode assessed via MINI and with a current QIDS-SR >10
5. Current episode of depression failed to have responded to adequate trials, or lack of tolerability or patient declined/clinically inappropriate, of two different NICE recommended medications (quetiapine, olanzapine (with or without fluoxetine), lamotrigine) or lurasidone. Adequacy of treatment trial defined using a custom-designed 'Bipolar Demographics and Treatment Questionnaire' (BDTQ).
6. Aged 18 years or over at the point of consent
7. Willing and able to provide written informed consent prior to any trial procedures taking place
8. In the opinion of the investigator, is able to follow the trial prescription instructions and is able to manage 8 weeks supply of trial medication without risk of overdose
9. The patient, if female and of child-bearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)]
10. Women of child-bearing potential are required to use a highly effective contraceptive method during the pre-randomisation and post-randomisation phase of the trial. Highly effective methods of contraception include:
- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
- bilateral tubal occlusion
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject)

Stage 2/ at randomisation:
1. Been in Stage 1 (pre-randomisation) for a minimum of 23 calendar days.
2. Currently depressed, i.e. meeting DSM-5 (78) criteria for a Major Depressive Episode and with a current QIDS-SR >10.
3. A minimum of two telephone/teleconference or videoconference calls with a trial RA and two on-line weekly symptom ratings have been completed during the pre-randomisation phase
4. On mood stabilising medication (lithium, valproate, carbamazepine, lamotrigine)
5. If on an antipsychotic this must be one listed, and at a dose of no more than the maximum stated, in the table in section 4.1.

6. All regular psychotropic medication, including antipsychotics and mood stabilisers, at a stable dose for a minimum of four weeks. Additionally, if a participant is on lamotrigine, quetiapine, olanzapine or lurasidone then this must have been at the current dose or higher for a minimum of three months.
7. The patient, if female and of child-bearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)]*.
8. Women of child-bearing potential are required to use a highly effective contraceptive method during the post-randomisation phase of the trial. Highly effective methods of contraception include:
8.1. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
8.2. progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
8.3. intrauterine device (IUD)
8.4. intrauterine hormone-releasing system (IUS)
8.5. vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
8.6. bilateral tubal occlusion
8.7. sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject)
9. Willing and able to confirm written informed consent at the point of randomisation, after the pre-randomisation period.

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Previous inclusion criteria as of 12/10/2020:

Stage 1/ pre-randomisation:
1. Currently under the care of secondary care mental health services at screening with a plan for the patient to remain in secondary care throughout the period of the trial
2. A decision made by the patient's clinical team that a change in medication is indicated
3. A current diagnosis of Bipolar Disorder (type I or II), defined as in DSM-5, which is supported by the use of the Mini-International Neuropsychiatric Interview (MINI)
4. Currently depressed, i.e. meeting DSM-5 criteria for a Major Depressive Episode assessed via MINI and with a current QIDS-SR >10
5. Current episode of depression failed to have responded to adequate trials, or lack of tolerability or patient declined/clinically inappropriate, of two different NICE recommended medications (quetiapine, olanzapine (with or without fluoxetine), lamotrigine) or lurasidone. Adequacy of treatment trial defined using a custom-designed 'Bipolar Demographics and Treatment Questionnaire' (BDTQ).
6. Aged 18 years or over at the point of consent
7. Willing and able to provide written informed consent prior to any trial procedures taking place
8. In the opinion of the investigator, is able to follow the trial prescription instructions and is able to manage 8 weeks supply of trial medication without risk of overdose
9. The patient, if female and of child-bearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)]
10. Women of child-bearing potential are required to use a highly effective contraceptive method during the pre-randomisation and post-randomisation phase of the trial. Highly effective methods of contraception include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
- bilateral tubal occlusion
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject)

Stage 2/ at randomisation:
1. Currently depressed, i.e. meeting DSM-5 (56) criteria for a Major Depressive Episode and with a current QIDS-SR >10.
2. A minimum of two telephone phone calls with a trial RA and two on-line weekly symptom ratings have been completed during the pre-randomisation phase
3. On mood stabilising medication (lithium, valproate, carbamazepine, lamotrigine)
4. All regular psychotropic medication, including mood stabilisers, at a stable dose for a minimum of four weeks
5. The patient, if female and of child-bearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)].
6. Women of child-bearing potential are required to use a highly effective contraceptive method during the post-randomisation phase of the trial. Highly effective methods of contraception include:
- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
- bilateral tubal occlusion
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject)
7. Willing and able to confirm written informed consent at the point of randomisation, after the pre-randomisation period.

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Previous inclusion criteria as of 20/05/2020:
Stage 1/ pre-randomisation:
1. Currently under the care of secondary care mental health services at screening with a plan for the patient to remain in secondary care throughout the period of the trial.
2. A decision made by the patient's clinical team that a change in medication is indicated.
3. A current diagnosis of Bipolar Disorder (type I or II), defined as in DSM-5, which is supported by the use of the Mini-International Neuropsychiatric Interview (MINI) (55).

4. Currently depressed, i.e. meeting DSM-5 criteria for a Major Depressive Episode assessed via MINI and with a current QIDS-SR >10.
5. Current episode of depression failed to have responded to adequate trials, or lack of tolerability or patient declined/clinically inappropriate, of two different NICE recommended medications (quetiapine, olanzapine + fluoxetine, lamotrigine) or lurasidone. Adequacy of treatment trial defined using a custom designed 'Bipolar Demographics and Treatment Questionnaire' (BDTQ).
6. Aged 18 or over at the point of consent.
7. Willing and able to provide written informed consent prior to any trial procedures taking place.
8. In the opinion of the investigator, is able to follow the trial prescription instructions and is able to manage 8 weeks supply of trial medication without risk of overdose.
9. The patient, if female and of child-bearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)].
10. Women of child-bearing potential are required to use a highly effective contraceptive method during the pre-randomisation and post-randomisation phase of the trial. Highly effective methods of contraception include:
- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
- bilateral tubal occlusion
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject)
Stage 2/ at randomisation:
1. Currently depressed, i.e. meeting DSM-5 (56) criteria for a Major Depressive Episode and with a current QIDS-SR >10.
2. A minimum of two telephone phone calls with a trial RA and two on-line weekly symptom ratings have been completed during the pre-randomisation phase
3. On mood stabilising medication (lithium, valproate, carbamazepine, lamotrigine)
4. All regular psychotropic medication, including mood stabilisers, at a stable dose for a minimum of four weeks
5. The patient, if female and of child-bearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)].
6. Women of child-bearing potential are required to use a highly effective contraceptive method during the post-randomisation phase of the trial. Highly effective methods of contraception include:
- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
- bilateral tubal occlusion
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period

of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject)
7. Willing and able to confirm written informed consent at the point of randomisation, after the pre-randomisation period.

Previous inclusion criteria:

Stage 1/ pre-randomisation:
1. Currently under the care of secondary care mental health services at screening with a plan for the patient to remain in secondary care throughout the period of the trial
2. A decision made by the patient's clinical team that a change in medication is indicated
3. A current diagnosis of Bipolar Disorder (type I or II), defined as in DSM-5, which is supported by the use of the Mini-International Neuropsychiatric Interview (MINI)
4. Currently depressed, i.e. meeting DSM-5 criteria for a Major Depressive Episode assessed via MINI and with a current QIDS-SR > 10
5. Current episode of depression failed to have responded to adequate trials, or lack of tolerability or patient refusal, of two different NICE recommended medications (quetiapine, olanzapine + fluoxetine, lamotrigine) or lurasidone. Adequacy of treatment trial defined using a custom designed 'Bipolar Depression Treatment Questionnaire' (BDTQ)
6. Aged 18 or over at the point of consent
7. Willing and able to provide written informed consent prior to any trial procedures taking place
8. In the opinion of the investigator, is able to follow the trial prescription instructions and is able to manage 8 weeks supply of trial medication without risk of overdose
9. The patient, if female and of child-bearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)]
10. Women of child-bearing potential are required to use a highly effective contraceptive method during the pre-randomisation and post-randomisation phase of the trial. Highly effective methods of contraception include:
10.1 Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
10.2. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
10.3. Intrauterine device (IUD)
10.4 Intrauterine hormone-releasing system (IUS)
10.5. Vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
10.6. Bilateral tubal occlusion
10.7. Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject)

Stage 2/ at randomisation:
1. Currently depressed, i.e. meeting DSM-5 (53) criteria for a Major Depressive Episode and with a current QIDS-SR > 10
2. A minimum of two telephone phone calls with a trial RA and two on-line weekly symptom ratings have been completed during the pre-randomisation phase
3. On mood stabilising medication (lithium, valproate, carbamazepine, lamotrigine)

4. All regular psychotropic medication, including mood stabilisers, at a stable dose for a minimum of four weeks
5. The patient, if female and of childbearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)
6. Women of child-bearing potential are required to use a highly effective contraceptive method during the post-randomisation phase of the trial. Highly effective methods of contraception include:
6.1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
6.2. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
6.3. Intrauterine device (IUD)
6.4. Intrauterine hormone-releasing system (IUS)
6.5. Vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
6.6. Bilateral tubal occlusion
6.7. Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject)
7. Willing and able to confirm written informed consent at the point of randomisation, after the pre-randomisation period

Qualitative interviews
A sample of participants who opt to consent to qualitative interviews will be contacted. For staff interviews, a sample of PIs at sites that have been open to recruitment for at least 4 months, and are willing to be interviewed, will be contacted.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
90

Key exclusion criteria
Current exclusion criteria as of 29/07/2022:

Stage 1/ pre-randomisation:
1. DSM-5 defined severe substance use disorder.
2. Current psychotic symptoms as assessed using the MINI.
3. History of retinal disease.
4. Current cardiovascular symptoms or significant concerns around cardiovascular disease.
5. History of significant renal disease (for example within the last 6 months eGFR is less than 50ml/min/1.73m2 or there is a concern that eGFR is deteriorating and may be expected to fall below 50 during the course of the study).
6. Any known sensitivity to trial drug including its excipients.
7. Current pregnancy or planned pregnancy during the trial period, or breastfeeding.
8. Starting specific psychotherapy from four weeks before randomisation through to Week 12 post-randomisation.
9. Currently taking part in another clinical trial that would interfere with the outcomes of PAX-BD (site team to check with the CI and Trial Management Group if in doubt).
10. Confirmed diagnosis with potential confounding factors such as Parkinson's disease, restless leg syndrome (where restless legs syndrome has been formally diagnosed by a sleep clinic).
11. Significant clinical concern regarding impulse control behaviours

Stage 2/ at randomisation:
1. Psychotic symptoms over the preceding 4 weeks.
2. Any known sensitivity to trial drug including its excipients
3. Any deterioration in physical or mental health since pre-randomisation that means there is a clinical concern to proceed with the study.
4. Current or planned pregnancy during the trial period, or breast feeding.
5. Starting specific psychotherapy from four weeks before randomisation through to Week 12 post-randomisation.
6. Currently taking part in another clinical trial that would interfere with the outcomes of PAX-BD (site team to check with the CI and Trial Management Group if in doubt).
7. Confirmed diagnosis with potential confounding factors such as Parkinson's disease, restless leg syndrome (where restless legs syndrome has been formally diagnosed by a sleep clinic).
8. Significant clinical concern regarding impulse control behaviours
9. Electroconvulsive therapy (ECT) in the last 28 days.
10. Any study team's concern regarding the patient's ability to remain engaged in the study collecting self-ratings of their symptoms and undertake all study procedures.

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Previous exclusion criteria as of 20/05/2020:

Stage 1/ pre-randomisation:
1. DSM-5 defined severe substance use disorder.
2. Current psychotic symptoms as assessed using the MINI.
3. History of retinal disease.
4. Current cardiovascular symptoms or significant concerns around cardiovascular disease.
5. History of significant renal disease (for example within the last 6 months eGFR is less than 50ml/min/1.73m2 or there is a concern that eGFR is deteriorating and may be expected to fall below 50 during the course of the study).
6. Any known sensitivity to trial drug including its excipients.
7. Current pregnancy or planned pregnancy during the trial period, or breastfeeding.
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BD (site team to check with the CI and Trial Management Group if in doubt).
10. Confirmed diagnosis with potential confounding factors such as Parkinson's disease, restless leg syndrome (where restless legs syndrome has been formally diagnosed by a sleep clinic).
11. Significant clinical concern regarding impulse control behaviours

Stage 2/ at randomisation:
1. Psychotic symptoms over the preceding 4 weeks.
2. Any known sensitivity to trial drug including its excipients
3. Any deterioration in physical or mental health since pre-randomisation that means there is a clinical concern to proceed with the study.
4. On an antipsychotic at the point of randomisation.
5. Current or planned pregnancy during the trial period, or breast feeding.
6. Starting specific psychotherapy from four weeks before randomisation through to Week 12 post-randomisation.
7. Currently taking part in another clinical trial that would interfere with the outcomes of PAX-BD (site team to check with the CI and Trial Management Group if in doubt).
8. Confirmed diagnosis with potential confounding factors such as Parkinson's disease, restless leg syndrome (where restless legs syndrome has been formally diagnosed by a sleep clinic).
9. Significant clinical concern regarding impulse control behaviours
10. Any study team's concern regarding the patient's ability to remain engaged in the study collecting self-ratings of their symptoms.

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Stage 1/ pre-randomisation:
1. DSM-5 defined severe substance use disorder
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11. Clinical concern of previous impulse control behaviours including harmful alcohol or drug use, binge eating, gambling or sexual behaviours, or regarding significant suicidal risks

Stage 2/ at randomisation:
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2. Any known sensitivity to trial drug including its excipients
3. Any deterioration in physical or mental health since pre-randomisation that means there is a clinical concern to proceed with the study
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5. Current or planned pregnancy during the trial period, or breastfeeding
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9. Clinical concern of previous impulse control behaviours including harmful alcohol or drug use, binge eating, gambling or sexual behaviours or regarding significant suicidal risks
10. Any study team's concern regarding the patient's ability to remain engaged in the study collecting self-ratings of their symptoms

Date of first enrolment
30/09/2019

Date of final enrolment
14/06/2022

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust
St. Nicholas Hospital
Jubilee Road
Gosforth
Newcastle Upon Tyne
United Kingdom
NE3 3XT

Study participating centre
Nottinghamshire Healthcare NHS Foundation Trust
The Resource, Trust HQ
Duncan Macmillan House
Porchester Road
Nottingham
United Kingdom
NG3 6AA

Study participating centre
Surrey and Borders Partnership NHS Foundation Trust
18 Mole Business Park

Randalls Road
Leatherhead
United Kingdom
KT22 7AD

Study participating centre
Avon And Wiltshire Mental Health Partnership NHS Trust
Jenner House
Avon Way
Langley Park
Chippenham
United Kingdom
SN15 1GG

Study participating centre
Derbyshire Healthcare NHS Foundation Trust
Trust Headquarters
Kingsway Hospital
Kingsway
Derby
United Kingdom
DE22 3LZ

Study participating centre
Oxford Health NHS Foundation Trust
Warneford Hospital
Warneford Lane
Headington
Oxford
United Kingdom
OX3 7JX

Study participating centre
Cheshire and Wirral Partnership NHS Foundation Trust
Trust Board Offices
Upton Lea Resource Centre
The Countess Of Chester Health Park
Chester
United Kingdom
CH2 1BQ

Study participating centre
Devon Partnership NHS Trust
Wonford House Hospital
Dryden Road
Exeter
United Kingdom
EX2 5AF

Study participating centre
Leicestershire Partnership NHS Trust
Riverside House
Bridge Park Plaza
Bridge Park Road
Thurmaston
Leicester
United Kingdom
LE4 8PQ

Study participating centre
Lincolnshire Partnership NHS Foundation Trust
Unit's 8 & 9
The Point
Lions Way
Sleaford
United Kingdom
NG34 8GG

Study participating centre
South West Yorkshire Partnership NHS Foundation Trust
Trust Headquarters
Fieldhead
Ouchthorpe Lane
Wakefield
United Kingdom
WF1 3SP

Study participating centre
Sheffield Health & Social Care NHS Foundation Trust
Fulwood House
Old Fulwood Road
Sheffield
United Kingdom
S10 3TH

Study participating centre
South London and Maudsley NHS Foundation Trust
Maudsley Hospital
Denmark Hill
London
United Kingdom
SE5 8AZ

Study participating centre
Essex Partnership University NHS Foundation Trust
The Lodge
Runwell Chase
Runwell
Wickford
United Kingdom
SS11 7XX

Study participating centre
NHS Tayside
Ninewells Hospital and Medical School
James Arrott Drive
Dundee
United Kingdom
DD1 9SY

Study participating centre
NHS Lothian
Waverley Gate
2-4 Waterloo Place
Edinburgh
United Kingdom
EH1 3EG

Study participating centre
NHS Greater Glasgow and Clyde
J B Russell House
Gartnavel Royal Hospital
1055 Great Western Road

Glasgow
United Kingdom
G12 0XH

Study participating centre
Tees, Esk and Wear Valleys NHS Foundation Trust
West Park Hospital
Darlington
United Kingdom
DL2 2TS

Study participating centre
Lancashire & South Cumbria NHS Foundation Trust
Unit 5
Sceptre Point
Sceptre Way
Preston
United Kingdom
PR5 6AW

Study participating centre
Kent and Medway NHS and Social Care Partnership Trust
Canada House
Barnsole Road
Gillingham
United Kingdom
ME7 4JL

Sponsor information

Organisation
Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust

ROR
https://ror.org/01ajv0n48

Funder(s)

Funder type

Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 16/154/01

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/02/2025	29/04/2025	Yes	No
Results article		01/05/2025	05/06/2025	Yes	No
Protocol article		05/07/2021	07/07/2021	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Plain English results	version 01	11/01/2024	26/07/2024	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes