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Noradrenaline treatment of apathy and impulsivity in participants with Progressive Supranuclear Palsy syndromes

Submission date
01/02/2021

Recruitment status
No longer recruiting

Registration date
08/02/2021

Overall study status
Completed

Last Edited
30/07/2025

Condition category
Nervous System Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The illness Progressive Supranuclear Palsy (PSP) is best known for its effect on movement and balance, but it also causes apathy and impulsivity. These behavioural changes can have a big impact on the quality of life for patients and their carers. There is evidence that these behavioural changes are caused, in part, by a loss of the brain's natural adrenaline (called noradrenaline). This new clinical trial is designed to restore the levels of noradrenaline, using a drug called atomoxetine. This clinical trial aims to look at the safety and tolerability of atomoxetine in people with PSP.

Who can participate?
People with PSP (supported by their family member/carer) recruited from NHS hospitals in the UK

What does the study involve?
Stage 1: At the first study visit (visit 1), participants will be given information about the study to read, participants will then be invited to provide consent (agreement) to participate, alongside one of their family members/carers (called a research partner). The study team will make sure that there are no safety or health concerns for participants taking part. Participants also have the option to undertake an MRI scan and/or give blood for genetic analysis.

Stage 2: Participants will be allocated, with an equal chance (like tossing a coin), to receive either the study drug (atomoxetine) or a placebo (a “dummy pill” designed to look like atomoxetine but without any active ingredients) for 8 weeks. Participants and their research partners will be asked to visit the study centre at the beginning (visit 2) and at the end of this period (visit 3), and to take the study medication in between these visits. At visit 2 and 3, a number of tests and questionnaires will be completed by participants or their research partners about PSP symptoms.

Stage 3: Participants will take 2 weeks rest from the study medication, where they will just be on their normal medication (if any).

Stage 4: Participants will switch to either placebo or atomoxetine so that they receive the treatment/intervention that they did not receive in stage 2 of the study. All participants will receive atomoxetine at some point during the study. Participants and their research partners will complete visits at the start (visit 4) and the end (visit 5) of the 8 week period and answer the same questionnaires as in stage 2.

Stage 5: Participants and their research partners will be asked to attend a final study visit (visit 6) 4 weeks after finishing the medication in stage 4. Participants and their research partners will be asked, to complete some final tests and questionnaires at visit 6.

What are the possible benefits and risks of participating?
There is no guarantee that participants will benefit from taking part in this study. However, information collected as part of their participation may benefit patients with PSP in the future and participants will have made an important contribution to our understanding of PSP and the effects of the trial medication on the brain.

The dose of atomoxetine used in the study is the dose normally used to treat other patients in the clinic. It is usually well-tolerated, but as with all medications, there is a chance of side effects.

Where is the study run from?
The study is based at the University of Cambridge (UK) and Cambridge University Hospitals NHS Foundation Trust (UK) with management by the Norwich Clinical Trials Unit at the University of East Anglia (UK)

When is the study starting and how long is it expected to run for?
From January 2021 to September 2025

Who is funding the study?
Cambridge Centre for Parkinson-plus (CCPP) (UK) and the Medical Research Council (UK)

Who is the main contact?
1. Prof James Rowe (Chief Investigator)
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2. Estelle Payerne (Trial Manager)
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-004472-19

Integrated Research Application System (IRAS)
272063

Protocol serial number
CPMS 44441, IRAS 272063

Study information

Scientific Title
A randomised, double-blind, placebo-controlled, crossover design, phase IIa clinical trial to evaluate the efficacy and safety of oral atomoxetine for the treatment of cognitive and behavioural change in participants with Progressive Supranuclear Palsy syndromes

Acronym
NORAPS

Study objectives
An 8 weeks atomoxetine treatment (a selective noradrenaline reuptake inhibitor) will be safe and well-tolerated by people with Progressive Supranuclear Palsy (PSP) and will improve apathy

and impulsivity compared to 8 weeks placebo. A good risk to benefit ratio, and limited adverse events outside of those expected in people with PSP, are anticipated

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 06/01/2021, South Central- Oxford B Research Ethics Committee (The Deanery, Christ Church, St Aldate's, Oxford, OX1 1DP; +44 (0)207 104 8235/8270; oxfordb.rec@hra.nhs.uk), ref: 20/SC/0416

Study design
Multi-centre double-blind placebo-controlled randomized crossover Phase IIb study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Progressive supranuclear palsy

Interventions
This trial will use a randomised crossover design to compare the effects of 8 weeks oral solution atomoxetine (40 mg taken as 10 ml of 4 mg/ml oral solution once daily) compared to 8 weeks placebo, with a 2 week washout period, on impulsivity and apathy, in 84 patients diagnosed with Progressive Supranuclear Palsy (PSP).

Potential participants will be identified in several ways including from the NHS clinics at participating sites and referrals (primary and secondary care). Potential participants identified will be informed about the trial by their clinical care team and, if interested to know more, given a detailed study-specific patient information sheet (PIS). Potential participants interested in taking part will then be invited to the screening/baseline visit where informed consent will be taken before assessing and confirming their eligibility to the trial as described below.

At the baseline/screening visit (visit 1), interested potential participants will be offered an appointment for safety screening and baseline assessment. Written informed consent will be obtained and eligibility will be confirmed through clinical/safety assessments. Research partners will be identified by the potential participant and approached and recruited face-to-face in the clinic, if accompanying the participant, or remotely, if not possible in the clinic. In this case, the research partner will be first approached by the potential participant using an invitation letter and if interested a PIS provided by the study team. Recruitment of potential research partners can also take place remotely using posted consent forms, with a telephone discussion. Safety screening will include a comprehensive health assessment of vital signs, safety blood tests (including folicle stimulating hormone and/or serum pregnancy test if required), and completion of the Columbia-Suicide Severity Rating Scale (CSSRS). Potential participants presenting with a risk of cardiovascular disease (including family history) will be asked to undergo an electrocardiogram (ECG). The potential participant’s medical history will be collected and recorded as well as the concomitant medication taken. In addition to the confirmation of the inclusion and exclusion criteria, the baseline assessments will include a neurological examination

by a medically trained consultant neurologist to confirm PSP diagnosis. The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Progressive Supranuclear Palsy Rating Scale (PSP_RS), and Progressive Supranuclear Palsy Clinical Deficits Scale (PSP_CDS) clinician-rated scales will also be used for assessment. Where participants have given additional consent, genetics (DNA) analyses will be performed. For participants who also have given additional consent, an optional MRI scan (or two at sites with both 3T and 7T MRI scanners) will be done.

Once eligibility is confirmed and all pre-designated questions are completed in the case report form, the local research staff will then have access to the randomisation process for that participant. Eligible consented participants will be randomised on a 1:1 basis to one of the two trial crossover arms using a web based randomisation process. The randomisation code will be saved in the study database for later decoding and also for emergency unblinding purposes.

After randomisation participants will start treatment phase 1 (visit 2), which will occur at the earliest convenience, but within 28 days from baseline. Re-screening may be considered by the local investigator if the delay from visit 1 to visit 2 exceeds 6 weeks, or if other significant changes in health become known to the study team. At visit 2, participants will undergo safety and clinical/neuropsychological assessments. These will include:
1. Changes to concomitant medications
2. Recording of vital signs
3. Safety blood test (and urine pregnancy test if required)
4. Completion of CSSRS
5. Recording of adverse events
6. Neuropsychological assessment using Cambridge Behavioural Inventory Revised (CBI-R) impulsivity and motivation composite subscores, Cambridge Questionnaire for Apathy and Impulsivity Traits (CamQUAIT), Connor’s Adult ADHD Rating Scale (CAARS) Short-Form sub scores completed by both the patient and research partner, Progressive Supranuclear Palsy Quality of Life scale (PSP-QoL) completed by both the patient and research partner, Hospital Anxiety and Depression Scale (HADS), Clinical Global Impression of Severity (CGI-S), Progressive Supranuclear Palsy Rating Scale (PSP_RS), Frontal Assessment Battery (FAB), Montreal Cognitive Assessment (MoCA), Repeatable Battery for the Assessment of Neuropsychological Disease Severity (RBANS), and the clinician rated StopSsignal Task (SST)

The first dose of either the study drug or placebo will then be administered to the patient, who will be asked to stay at the clinical research facility/clinic for blood to be taken approximately 2 h later (minimum of 90 min) for pharmacodynamics analysis (PK). An ECG will be undertaken during that time (1 to 3 h from first dosing).

Following visit 2, participants will be asked to take an oral dose of the study drug (atomoxetine or placebo) once in the morning for 8 weeks. Participants will be asked to take their medication at the same time each day and to document this in their compliance booklets (Diary). This diary will also be used to records any falls happening over the duration of the trial.

Approximately 4 weeks after commencing a treatment phase, participants will require additional medication. This can be collected by the participant or their research partner from the hospital pharmacy (to allow the return of the previously dispensed bottles where possible) or exceptionally, couriered directly to patients. Prior to additional medication being dispensed, carers should be contacted by the site via telephone for compliance to be documented and for a short assessment of aderse events (AEs) to be undertaken. Site staff will also ensure that the dispensed bottles are being used in the correct order to ensure that no out-of-date study medication is accidentally used.

At the end of the first treatment phase, after receiving the study medication for 8 weeks, participates will be invited for assessment (visit 3). Patients will undergo safety/clinical /neuropsychological assessments consistent with the visit 1. These will include:
1. Changes to concomitant medications
2. Recording of vital signs
3. Safety blood test (and urine pregnancy test if required)
4. Recording of adverse events
5. Neuropsychological assessment using CBI_R (impulsivity and motivation composite subscores), CamQUAIT, CAARS (short form sub-scores – patient and carer), PSP-QoL (patient and carer), HADS, CGI-S, PSP_RS, FAB, MoCA, RBANS and SST

Following visit 3, there will be a washout period of 2 weeks minimum, where no study medication is to be taken.

After the 2 week washout period, participants will start treatment phase 2 (visit 4). Before receiving the first dose of the treatment they did not recive during treatment phase 1, participants will undergo safety assessments and clinical/neuropsychological assessments consistent with the start of treatment visit (Visit 2). All neuropsychology assessments and tests from Visit 2 will also be repeated at this time point. The first dosing of the cross-over treatment phase (atomoxetine or placebo) will then take place and will be followed with the undertaking of an ECG (1 to 3 h later) and blood tests (for PK analysis at approximatively 2 h). Participants will then be asked to take the study drug (cross-over treatment) in the same way as during the treatment phase 1 (once daily for 8 weeks) and to record this in their compliance booklets (Diary, including the recording of falls not resulting in paramedical review/A&E attendance /hospitalisation).

Additional medication dispensing will take place approximately 4 weeks after visit 4, as per the treatment phase 1, with documentation of compliance, AE assessment, and confirmation of correct order of use of the bottles dispensed.

At the end of treatment phase 2, 8 weeks after visit 4, participants will be invited to the study centre (Visit 5) to undergo safety/clinical/neuropsychological assessments consistent with visit 3. They will also be asked to return the study drug bottles (empty or not) and their medication and fall diary at this visit so that falls and medication compliance can be recorded.

A final visit (visit 6) will be undertaken 4 weeks later. The research partner and patient rated questionnaires undertaken previously will be repeated at this time point in addition of all safety monitoring assessments (e.g. vital signs, safety blood test, and urine pregnancy test if required).

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
1. Efficacy measured using the Cambridge Behavioural Inventory Revised Apathy-Impulsivity Composite Score (CBI-R-I) at 0, 8, 10, and 18 weeks

2. Safety assessed using the numbers and percentages of deaths and unique participants with adverse events (AEs) and serious adverse events (SAEs) leading to discontinuation between 0 and 22 weeks
3. Tolerability assessed using the numbers of adverse events (AEs) and adverse reactions (ARs), including serious AEs and ARs between 0 and 22 weeks

Key secondary outcome(s))
1. Global clinical improvement measured using the Clinical Global Impression of Change (CGI-C) at 8 and 18 weeks and the Clinical Global Impression of severity (CGI-S) at 0 and 10 weeks
2. Behaviour and cognition measured using the Cambridge Behavioural Inventory Revised (CBI-R) total score, and Cambridge Questionnaire for Apathy and Impulsivity Traits (CamQUAIT) apathy score completed by the research partner at 0, 8, 10, 18, and 22 weeks
3. Cognitive and behavioural functioning measured using the Connor's Adult ADHD Rating Scale (CAARS) Short-Form sub scores completed by both the patient and research partner at 0, 8, 10, 18, and 22 weeks
4. Anxiety and depression measured using the patient-rated Hospital Anxiety and Depression Scale (HADS) at 0, 8, 10, 18, and 22 weeks
5. Patient and carer (research partner) quality of life measured using the Progressive Supranuclear Palsy Quality of Life scale (PSP-QoL) at 0, 8, 10, 18, and 22 weeks
6. General measures of cognitive functioning measured using the clinician-rated Repeatable Battery for the Assessment of Neuropsychological Disease Severity (RBANS) which includes verbal fluency) at 0, 8, 10, and 18 weeks

Exploratory outcome measures:
1. Cognition measured using the clinician-rated Montreal Cognitive Assessment (MoCA) at 0, 8, 10, and 18 weeks
2. Severity of PSP and disease progression measured using the clinician-rated Progressive Supranuclear Palsy Rating Scale (PSP_RS) at baseline, 0, 8, 10, and 18 weeks
3. Influence of baseline clinical deficit on response to atomoxetine measured using the clinician-rated the Progressive Supranuclear Palsy Clinical Deficits Scale (PSP_CDS) at baseline
4. Executive function is measured using the clinician-rated the Frontal Assessment Battery (FAB) at 0, 8, 10, and 18 weeks
5. Response inhibition is measured using the clinician-rated stop-signal task (SST) at 0, 8, 10, and 18 weeks
6. Influence of genetic variations on response to atomoxetine, including but not limited to, differences in treatment response and tolerability evaluated according to CYP2D6 polymorphism (poor metaboliser versus extensive metaboliser) and NET/SLC6A2 polymorphism from optional blood samples for DNA extraction collected at baseline
7. Treatment response and tolerability measured using plasma levels of atomoxetine at at 0 and 8, or 10 and 18 weeks (depending on arm of crossover study)
8. Influence of structural integrity of the brain, including locus coeruleus (the main source of brain noradrenaline) measured by high-field (3T) and ultra-high-field (7T) optional MRI imaging at basline (optional)
9. Influence of atomoxetine on heart rate variability measured by electrogradiogram (ECG) undertaken 1 to 3 h after the initial dose of atomoxetine at 0 and 10 weeks

Completion date
30/09/2025

Eligibility

Key inclusion criteria
People with Progressive Supranuclear Palsy (PSP):
1. Have the mental capacity to give informed consent for participation in the study
2. Have a diagnosis of probable or possible Richardson's Syndrome (PSP-RS), PSP with predominant frontal presentation (PSP-F), PSP with predominant speech/language disorder (PSP-SL), or PSP with corticobasal syndrome (PSP-CBS) variant under the International Parkinson and Movement Disorder Society (MDS) criteria. Patients with an initial diagnosis of progressive gait freezing (PGF) but currently presenting as PSP may also be included.
3. Aged between 50 and 85 years
4. Have a 'research partner', such as a relative, unpaid or paid carer, or a care home manager, who has a minimum of once-a-week telephone or face-to-face contact and is able, and consents, to provide information on proxy measures
5. Receiving stable psycho-active medications (such as L-DOPA, dopaminergic agonist, anti-cholinergic, amantadine, other anti-parkinsonian medication, anti-depressants, or any other psychoactive medication) for at least 28 days from visit 1 with no ramping up or weaning off medications
6. Able to take part in this study
7. Not pregnant, surgically sterile, or postmenopausal. Premenopausal patients can be included but will undergo pregnancy tests (at screening and at visits 2 to 5) to confirm that they are not pregnant. Surgically sterile is defined as having had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 6 weeks prior to enrolment. A postmenopausal state is defined as no menses for 12 months without alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Research partner:
1. A minimum of once-a-month face-to-face or telephone contact with the main study participant
2. Able to provide information on proxy measures
3. Aged ≥16 years

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
16 years

Sex
All

Key exclusion criteria
People with Progressive Supranuclear Palsy (PSP):
1. Use of monoamine oxidase inhibitor, SNRI, or other drugs that alter monoamine concentrations (including tricyclic antidepressants with the exception of low dose amitriptyline ≤ 30mg), systemic pressor agents, and any other medication that in the view of the PI would

contraindicate participation within 2 weeks of visit 1
2. Use of high dose (>10 mg) systemic steroids (such as prednisolone). Topical steroid and low dose systemic steroid use are acceptable even if taken long term.
3. Presence of significant cardiovascular disease such as ischaemic heart disease, cardiac rhythm abnormalities, or other clinically significant non-ischemic cardio-vascular disease. If at risk, including those with a family history of ischemic heart disease (parent with heart failure at 30 to 50 years) will undergo an electrocardiogram (ECG) at baseline to confirm eligibility.
4. Narrow (acute) angle glaucoma
5. History of, or current, pheocromocytoma
6. Known hepatic or renal failure (ALT or AST over three times reference range and total birulin >2 times the reference range; eGFR <60 ml/min; and/or serum creatinine >168 mol/l).
7. Presence or history of a medical condition that the PI feels may interfere with the participant's ability to comply with study instructions, would place the participant at increased risk, or might confound the interpretation of the study results
8. History of cancer within 3 years of visit 1 with the exception of fully excised non-melanoma skin cancers or non-metastatic prostate cancer
9. Presence of significant neurological (other than PSP) or psychiatric disorders including any psychotic disorder, clinically significant depression, suicidal thoughts or behaviour that are believed by the PI to represent a current safety risk (including a seizure within 3 years of visit 1 or history of recurrent seizures)
10. Known presence of a disease-associated mutation in genes known as C9ORF72, GRN, CHMP2B, TBK1, TARBP, or VCP or other frontotemporal lobar degeneration (FTLD) causative genes which are not associated with underlying tau pathology (individuals with MAPT mutations may participate if they meet all other eligibility criteria)
11. Any major surgery within 28 days of visit 1
12. Evidence of organ dysfunction or any clinically significant deviation from normal function in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population
13. Recent (in the last month) or current systemic infections (recent vaccination is not an exclusion criteria)
14. Current participation in any other clinical trial of an investigational medicinal product
15. Likely inability to give blood (such as fear of needles, etc.)
16. Insufficient proficiency in English to provide informed consent and to understand task instructions, as assessed by the clinical or study team
17. Body weight outside of the range 40 kg to 120 kg
18. Contraindications for MRI (only applicable for those consenting to MRI)
19. Breastfeeding
20. Any other contraindication to atomoxetine treatment as detailed in atomoxetine SmPC including, but not limited to, hypersensitivity to the active substance or to any of the excipients

Research partner:
1. Does not meet inclusion criteria

Date of first enrolment
16/04/2021

Date of final enrolment
31/05/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Addenbrookes Hospital
Hills Road
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Study participating centre
The Newcastle Upon Tyne Hospitals NHS Foundation Trust
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Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

Alternative Name(s)

Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Cambridge Centre for Parkinson-plus (CCPP)

Results and Publications

Individual participant data (IPD) sharing plan
Part, if not all, of the datasets generated during and/or analysed during the current study will be stored in publically available repositories (details will be made available at a later date).

IPD sharing plan summary
Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		28/07/2025	30/07/2025	Yes	No
HRA research summary			28/06/2023	No	No