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Predicting response to treatment in early Lewy body disease

Submission date
28/02/2023

Recruitment status
Recruiting

Registration date
17/04/2023

Overall study status
Ongoing

Last Edited
24/06/2024

Condition category
Nervous System Diseases

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

Plain English Summary
Background and study aims
Lewy body dementia (LBD) is a condition that effects thinking abilities and movement of affected individuals. Some people with LBD may benefit from treatment with a cholinesterase inhibitor, which affect a brain chemical system called the cholinergic system while others do not. The aim of this study is to develop a new test to identify which people with early stage Lewy Body Dementia (LBD) will respond best to treatments. A central feature of LBD is evidence of cholinergic loss, which contributes to symptoms like visual hallucinations, risk of falls, problems with walking and our ability to think, read and understand (cognition) the world around us.

One way to do this is to make use of electroencephalography (EEG). This is a method of recording brain signals using wires attached to a head cap; a completely pain free procedure, which allows the recording of changes in brainwaves. These changes might indicate whether someone could respond to a cholinergic treatment. We will give people with early stage LBD a short course of treatment with an established cholinergic drug called donepezil. Donepezil is also known as Aricept which you may be familiar with as a treatment for Alzheimer's disease and LBD. We will explore if there are changes in brainwaves in participants after being given donepezil. Participants will either get the real drug or a pretend (placebo) drug. We will see whether we can predict any improvements in thinking abilities based on visible changes in the EEG brainwaves.

Another way of putting it is that by identifying brainwave patterns we can attempt to predict which participant will benefit most from the study medication.

Who can participate?
We aim to enrol 60 participants with LBD and 16 healthy volunteers.

What does the study involve?
Participants will be randomly assigned (like flipping a coin) to receive either donepezil or a placebo for a certain period of time (with the exception of the healthy volunteers) followed by a period when no drug would be given before switching over to the other treatment group. Both donepezil and placebo will look exactly the same, hence both participants and researchers will not know at any point during the study whether they are receiving active treatment or placebo.

The medication being given in this study is normally used to treat certain conditions causing memory loss, it can slow down the progression of these conditions and cause memory to improve in some individuals. There are side effects that can happen with the treatment although most people tolerate this well.

We will also ask people to undergo a number of other tests including for example assessment of thinking abilities and memory. These assessments come under the umbrella terms of neurocognitive and neuropsychiatric testing and include drawing complex figures, reading aloud and problem solving but there are also questions related to personal feelings, mood and quality of life and some of these are addressed to the informal carer (like a spouse or close relative). It is essential for this study that we also conduct examination of the brain internally and we do this using two types of scanning, magnetic resonance imaging (MRI) and positron emission topography (PET). An MRI scan is used because it provides detailed structural images of the brain and we use PET scans to see the functioning of the brain. The PET scan uses a special dye containing radioactive tracers which will be delivered intravenously and will then highlight the specific areas of interest within the brain. A further element of this study protocol is the delivery of transcranial magnetic stimulation (TMS). This involves stimulation of the brain cells using a magnetic coil and it is also a completely pain free process. Its purpose is to inform us further of the cholinergic function of participants. A common symptom of LBD is a change in the way a person walks (gait). Participants will be assessed at the Gait lab and will undertake two tests walking around a short circuit and then repeating this while doing a task. These tests will be recorded and analysed. Following these assessments participants will then return home wearing a body sensor for a period of 7 days and this will record their levels of activity, gait, sleep and functional performance.

This will provide us with a very rich data set which may support the use of EEG as an easy to use way of identifying cholinergic function, permitting a more precise treatment approach for patients, which is currently lacking in this disease group.

What are the possible benefits and risks of participating?
Medication: The cholinesterase inhibitor Donepezil is normally used to treat certain conditions causing memory loss, it can slow down the progression of these conditions and cause memory to improve in some individuals. The possible adverse effects of donepezil are well established and include: Common or very common(up to 1 in 10): Aggression; agitation; decreased appetite; common cold; diarrhoea; dizziness; fatigue; gastrointestinal disorders; hallucination; headache; injury; muscle cramps; nausea; pain; skin reactions; sleep disorders; syncope; urinary incontinence; vomiting Uncommon (less than 1 in 100) Bradycardia; gastrointestinal haemorrhage; hypersalivation; seizure Rare or very rare (less than 1 in 1000) Cardiac conduction disorders; extrapyramidal symptoms; hepatic disorders; neuroleptic malignant syndrome; rhabdomyolysis Most people tolerate donepezil well.

Neurocognitive and neuropsychiatry tests: There is no adverse effect from these assessments. Doing these tests will take time for the participants and their care-givers. However, from our prior experience, many participants value the social interaction and engagement that being involved in a research study brings. We will make it more convenient for the participants by conducting a home visit so that this can be done in the comfort of their homes and paced according to their ability/availability. In a similar study using similar test battery, it took approximately two hours for the tests to be completed. These tests were well received by the participants and their care-givers.

MR scanning: Using the MRI Centre in the Institute for Ageing and Health, which has highly experienced staff who have been involved in many MR Imaging projects previously and have

examined many patients, helps assure safety. The questions asked of the patient and their carer or relative or other nominated person relating to c
ontraindications for MRI are verified, and repeated immediately prior to the MR scan. There are no known risks associated with the MR scan, and the scan is not painful. The only discomfort some people feel is claustrophobia whilst in the scanner and that they will need to lie still for the period of the scan (up to 40 minutes).

EEG testing: EEG testing will be applied by trained staff who have had previous experience of the application of EEG in vulnerable patient groups such as children and people with cognitive impairments. The EEG testing is applied using a specially designed electrodes and head cap and all equipment is electrically tested as being safe. Minor risks from the EEG include some skin irritation from the electrode sites but the use of the special head caps minimises this and the procedure is not painful or discomforting in any way. In our previous studies using our EEG system, we had no adverse reactions (in > 200 participants).

Short latency afferent inhibition (SAI): SAI is a protocol that involved use of transcranial magnetic stimulation (TMS). TMS is usually safe and well tolerated. Common adverse effects include headache, discomfort at stimulation site, light-headedness, tingling, spasm or twitching of facial muscles. Very rare adverse effects include seizures, mania and hearing loss. These have been reported in participants with a prior history of these conditions. In addition, as peripheral nerve stimulation is employed during the SAI protocol, there may be pain or discomfort at the site of stimulation. In our previous studies SAI has been well tolerated with no reported adverse reactions (in > 150 participants).

We will alleviate anxiety from undergoing these procedures by explaining to the participants and addressing any concerns they may have. Our previous experience indicates that dementia participants and their carer or relative derive benefit from the additional contact with research staff, and from the sense of helping with research into these illnesses.

Where is the study run from?
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
June 2019 to June 2025

Who is funding the study?
NIHR Newcastle Biomedical Research Centre (UK)

Who is the main contact?
Dr John-Paul Taylor, john-paul.taylor@ncl.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof John-Paul Taylor

Contact details

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
270045

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 43617, IRAS 270045

Study information

Scientific Title
The Cholinergic ResponsE in Early lewy body Disease (CREED) Study

Acronym
CREED

Study hypothesis
One or more of our biomarkers will be altered in people with prodromal LBD. One or more of the biomarkers will associate with symptoms related to cholinergic deficits. One or more of the functional biomarkers (fMRI, EEG, SAI, gait) will demonstrate change after CHEI treatment in prodromal LBD. One or more of the biomarkers will predict response to a CHEI. Longitudinal biomarker changes in patients with prodromal LBD treated with a CHEI will associate with improvement in symptoms. Structural MRI and fMRI, electro-physiological and gait biomarkers will evidence quantitative relationships with FEOBV, a direct measure of pre-synaptic cholinergic integrity.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/02/2020, Newcastle & North Tyneside 1 REC (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 2071048255; newcastlenorthtyneside1.rec@hra.nhs.uk), ref: 20/NE/0025

Study design
Observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Condition
Dementia, Lewy body disease

Interventions
Briefly, after providing informed consent, participants will complete:
1. A screening assessment - determines suitability to be included in the study. Participants with possible cognitive impairment due to Lewy body dementia or Parkinson's Disease but do not have a cognitive test as part of clinical practice will be assessed with Montreal Cognitive Assessment (MoCA). The MoCA is an interview (paper and pen test) that will take approximately 10 minutes and will be conducted while the participants attend their usual NHS clinic appointment. The assessment aims to exclude participants with no cognitive impairment from the study.

2. A baseline assessment - Participants will undergo a baseline visit to assess study eligibility. This will include a detailed clinical review. We are looking for patients who have cholinergic dysfunction but are not taking a cholinesterase inhibitor. Participants will undergo neurocognitive and neuropsychiatric tests(involving one interview/questionnaire, lasting up to 170 minutes, conducted at participant's home).
Participants will an EEG (brain wave test) and blood tests (lasting 1 hour, at Clinical Ageing Research Unit [CARU], Campus for Ageing and Vitality). In a subset of patients (n=10) and controls (n=10) we will repeat the EEG on a different day to assess reliability of the index.

3. Randomisation - participants will be randomly assigned (like flipping a coin) to receive either donepezil (a cholinesterase inhibitor) or a placebo for 8 weeks followed by a period when no drug would be given (4 weeks) before switching over the other treatment group for 8 weeks. For example, if a participant is given donepezil in the initial period, he/she will receive placebo in the later stage and vice versa. Both donepezil and placebo will look exactly the same, hence both the participants and the researchers will not know at any point during the study whether they are receiving active treatment or placebo. Block randomisation will be used to ensure that 50% patients in each group receive active intervention followed by placebo and the other 50% placebo followed by active intervention. The
randomisation list will be held independent to the core study team, by Dr Sean Colloby, the

study statistician and the sponsor's pharmacy. Unblinding during the study will not be allowed except in emergency or at the interim analysis point (Month 20). Study personnel and participants will be unaware of treatment assignment.

Medication
The medication will be administered in 2 tablets/capsules (active or placebo) to allow for dose escalation. For active treatment, for the first four weeks of the intervention, participants will receive one placebo and one 5 mg donepezil tablet; for the next four weeks they will receive two 5 mg donepezil tablets (10mg total). If patients are unable to tolerate 10mg we will step down to 5mg and maintain at this dose.

4. Two biomarker assessments- this will be done twice after each 8-week treatment period and consist of
4a: Neurocognitive and neuropsychiatric tests (interview/questionnaire)-conducted at the participants' home, lasting approximately 105 minutes
4b: Procedures (conducted at CARU, in a single day. Some tests will be carried out in the morning and some in the afternoon, with plenty of time for breaks in between. Alternatively, if the participants prefer the tests to be scheduled over several shorter visits, we can arrange that as well). The following describes the procedures.

Resting and task EEG
This is a record of brain waves which will be conducted in CARU and should take approximately 45 minutes.
Participants will be asked to wear a cap on the head with wires attached to it. The wires function as sensors which will record the brain waves into a computer programme. Participants will be asked to open and close their eyes for a few minutes throughout the recording and perform a simple task on the computer (like pressing on a right or left button to indicate where arrows are pointing on the computer screen). The procedure is usually well-tolerated. Some people experience redness on the scalp which will be temporary, but it should not cause any pain.

Short afferent inhibition protocol (transcranial magnetic stimulation)
This procedure involves transcranial magnetic stimulation which is a way of stimulating brain activity using a magnetic coil, with a concurrent electrical nerve stimulation of one of the hands. A magnetic coil (looks like a small metal detector) will be placed on top of the head. Magnetic stimulation is usually well-tolerated and should not cause any pain. There may be twitching of the muscles of the neck or jaw during the procedure. Occasionally, people who undergo the procedure may complain of headache, discomfort at the scalp or dizziness later but this is usually mild and short lasting. Very rarely, the procedure had been reported to have caused seizure or hearing disturbance although this seems to have only happened in people who have prior history of seizures. The electrical nerve
stimulation of the hand is usually well-tolerated. There may be some discomfort at the stimulation site during the procedure.

Magnetic resonance imaging (MRI)
This is a type of brain scan which will take around 45 minutes. This brain scan is considered a very safe test. The only possible risk is that it may affect implanted medical devices such as a heart pacemaker. The technician routinely completes a checklist before the scan to ensure you are suitable to undergo the scan.
Participants will be asked to remove all jewellery and loose metal before going into the scanner. They will be asked to lie still on their back in the scanner. There is padding to make them more comfortable and they can have a blanket if they feel cold. The scanner can be noisy so they can have protective earplugs or earphones. There is an intercom system and an emergency buzzer if

they need to contact anyone during the scan. Experienced staff will be with them at all times. Participants may be asked to perform several tasks such as looking at some pictures and pushing buttons to answer questions (similar to the EEG task) while the brain scan is being recorded.

Gait assessment at gait lab
This is an assessment of gait which will be carried out in CARU. Participants will be asked to walk on a walkway while performing mental tasks. A video recording of their gait will be made to allow for further analysis.

Body sensors: gait, sleep, activity (1 week at home)
This is a wearable device which will be attached to the participants' lower back (just above the hip) and secured with an adhesive tape. The sensors will be worn for seven days at home and will record information on their activity, gait and sleep. The sensors are usually well accepted and will not interfere with their activities.

Blood tests
We will also take blood samples (approximately 20 mL) for cholinesterase levels at baseline and at each biomarker assessment visits (a total of 3 times). In addition, the participants will be asked if they agree for their blood samples to be stored in the Newcastle Biobank for future studies e.g. proteomic/genomic analyses. If participants are agreeable to this, they will provide a separate consent to have their blood samples stored. Ethics and NHS approvals have already been obtained for this approach (Newcastle Biobank, REC ref 17/NE/0361; HTA licence 12534, designate person Dr Chris Morris). Participants who consented for the genetic studies will be asked to provide one urine sample as well. This will allow enhanced future evaluation of the characteristics of participants who are more likely to respond to a CHEI.

Safety Monitoring
It has been confirmed by our regulatory authority (MHRA) that our proposed study is not a clinical trial of an investigational medicinal product. However, we will still operate the study using robust governance processes as defined by our Sponsor. Thus, safety for patient participants will also be assessed on the basis of adverse events, vital signs, electrocardiogram (ECG/EKG) and laboratory tests at baseline and at each assessment point during the study.

End of study treatment
Medication (active or placebo) will not be continued after the second biomarker assessment and any subsequent initiation of cholinesterase inhibitors treatment will be at the discretion of the participant’s clinical team.

5. Follow-up assessment at 6 months
If participants are treated with donepezil by the clinical team after the end of study treatment. We will conduct a follow up assessment 6 months after that. This will involve a neurocognitive /neuropsychiatric tests (paper and pen tests),lasting approximately 105 minutes, carried out at participants' home

Intervention Type
Other

Primary outcome measure
1. Biomarkers (EEG, blood tests) at baseline, 8 weeks and 16 weeks. Further biomarkers (MRI, Gait assessments, Short afferent inhibition (SAI) and wearable activity monitor) at 8 weeks and 16 weeks
2. Power of attention time, PoA, (summation of simple choice reaction and digit vigilance time

derived from the computerised attention battery) at baseline, 8 weeks and 16 weeks. These tests are repeated after six months if participants choose to continue active treatment
3. Cognitive function measured using Montreal Cognitive Assessment (MoCA) at baseline, 8 weeks and 16 weeks. This test is repeated after six months if participants choose to continue active treatment

Secondary outcome measures
1. Measures of cognitive fluctuations (clinical assessment of fluctuations scale) at baseline, 8 weeks and 16 weeks. This test is repeated after six months if participants choose to continue active treatment
2. Gait function (step-time variability, gait speed, fall frequency) completed at 8 weeks and 16 weeks
3. Neuropsychiatric symptoms (Neuropsychiatric inventory) completed at baseline, 8 weeks and 16 weeks. This test is repeated after six months if participants choose to continue active treatment

Overall study start date
01/06/2019

Overall study end date
30/06/2025

Eligibility

Participant inclusion criteria
1. Aged over 60 years
2. MoCA < 26
3. Lewy Body Disease with cognitive impairment (one of the following):
3.1. PD-MCI: Meeting Level 1 PD-MCI criteria (screening stage) and Level 2 PD-MCI criteria (baseline assessment stage) with deficits > 2 SD below normative levels, or
3.2. For LB-MCI: Meeting LB-MCI criteria, or
3.3. Mild PD dementia, or
3.4. Dementia with Lewy body
4. English as a first language or fluent command of the English language as defined by the assessor.
5. A spouse, close relative or well established carer to accompany the subject to act as an informant (minimum contact twice weekly) and ensure medication compliance
6. Cholinesterase inhibitor and memantine naïve (not on a Cholinesterase inhibitor or memantine for the preceding 3 months)
7. If on anti-parkinsonian regime to have been on a stable regimen for at least 2 months

Participant type(s)
Patient

Age group
Adult

Lower age limit
60 Years

Sex

Both

Target number of participants
Planned Sample Size: 46; UK Sample Size: 46

Participant exclusion criteria
1. History of significant cerebrovascular disease
2. Presence of major cerebrovascular disease on brain imaging (severe leukoaraiosis or infarcts in strategic areas)
3. Other neurological diseases which may cause cognitive impairment e.g. a diagnosis of progressive supranuclear palsy, multiple system atrophy, or corticobasal degeneration, according to accepted diagnostic criteria
4. Presence of major depression
5. Physical co-morbidities including: history of severe gastrointestinal ulceration, severe asthma or obstructive pulmonary disease; systolic hypotension (< 90 mmHg); bradycardia (< 50 beats per minute); sick sinus syndrome; atrial or atrioventricular conduction block; QT interval prolongation (> = 450 ms)
6. Use of cognitive enhancing medications (e.g. cholinesterase inhibitors, memantine)
7. High dose benzodiazepines, antipsychotics or anticonvulsants
8. Use of anticholinergics with significant central effects e.g. oxybutynin
9. Contraindications to MR scanning (e.g. inability to lie flat for 30 minutes, claustrophobia, inability to tolerate a previous similar procedure, MR incompatible pacemaker)
10. Severe kidney disease
11. History of deep brain stimulation
12. Unstable and/or significant medical comorbidity likely to interfere with compliance
13. Significant functional deficits likely to interfere with compliance
14. Severe parkinsonism (Hoehn and Yahr stage IV or above)
15. Hypersensitivity to donepezil or piperidine derivatives

Recruitment start date
28/02/2020

Recruitment end date
30/06/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Freeman Hospital
Newcastle Upon Tyne Hospital Trust
Freeman Road
High Heaton

Newcastle
United Kingdom
NE7 7DN

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Freeman Hospital
Freeman Road
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England
United Kingdom
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+44 191 2824522
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Sponsor type
Hospital/treatment centre

Website
http://www.newcastle-hospitals.org.uk/

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
NIHR Newcastle Biomedical Research Centre

Alternative Name(s)
Newcastle Biomedical Research Centre, Newcastle NIHR Biomedical Research Centre

Funding Body Type
Private sector organisation

Funding Body Subtype

Research institutes and centers

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
30/09/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request
john-paul.taylor@ncl.ac.uk

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?
Participant information sheet	version 6.0	23/02/2023	09/03/2023	No	Yes
HRA research summary			26/07/2023	No	No