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Understanding how increasing some of the brain's chemicals can help thinking and behaviour in people with Parkinson’s disease

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03/09/2020

Recruitment status
No longer recruiting

Registration date
03/09/2020

Overall study status
Completed

Last Edited
05/09/2020

Condition category
Nervous System Diseases

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

Plain English summary of protocol

Background and study aims
Brain function depends on naturally occurring chemicals (‘neurotransmitters’) that communicate between brain cells. Several of these are reduced in Parkinson’s disease. Dopamine is one of the important neurotransmitters for Parkinson’s disease, and many drugs aim to increase Dopamine levels (eg. Sinemet, Madopar). We believe that another chemical called Noradrenaline is also important in Parkinson’s disease. This study looks at the effects of taking a single dose of a medication (atomoxetine) that boosts Noradrenaline in people with Parkinson’s disease.

Atomoxetine is a drug classified as a “Noradrenaline reuptake inhibitor” which means that it increases the levels of Noradrenaline in the brain. It is licensed in the UK and the USA for treatment of disorders such as Attention Deficit Disorder, and has been used in many research studies in healthy adults here in Cambridge and elsewhere. In this study it will be given as a tablet, using the standard starting dose for adults (40mg). We discuss possible side effects, but a complete summary of the drug can be found at: www.medicines.ie/medicine/11666/SPC /Strattera/ using the brand name Strattera. Alternatively Prof Rowe can give you a printed version.

Some people should not take Atomoxetine, for example if you suffer from heart disease. We will therefore ask you in confidence about these and other medical problems before taking part.

Who can participate?
Patients with Parkinson’s disease can take part, if they are between the ages of 45 - 80 and English speaking. Some medications cannot be taken at the same time as the drug we are using, so some people may not be able to take part. The brain scan is also very sensitive to metal, so we do not include people who have a lot of metal inside them, such as pacemakers or some prosthetics, or those who have had a lot of dental work. The study team would discuss these criteria for taking part in the study before joining up.

What does the study involve?
If you would like to take part, we will check that it is safe for you to do so. We have a list of

things that make some patients unsuitable to participate, and a member of the research team will discuss these with you. For example, people with heart disease, stroke, brain damage or dementia would not take part in this study, and some types of medication would also rule out participation.

Only one of the study sessions would involve Atomoxetine. They would begin at the Wellcome Trust Clinical Research Facility (WTCRF) or the Herchel-Smith Building (HSB) both located at Addenbrooke's Hospital in Cambridge. Sessions may last up to five hours, including periods of rest. Participants should have normal vision, with glasses if necessary. If you require spectacles, please remember to bring them on both testing days. We try to arrange these sessions 2 weeks apart (minimum 1 week, max 8 weeks apart, according to your convenience and availability of facilities).

After arrival, we will do some paperwork and safety checks for the study. We will also measure your blood pressure. Depending on a volunteer's medical history, some people will also need a heart tracing (ECG) before taking the tablets. This is a simple test that the nurses would do. Then you will be given the tablets to swallow with water. These tablets might contain Atomoxetine, or they might contain a dummy tablet (placebo).

The two study days where you will take the atomoxetine or the placebo will follow a similar structure. This is outlined below:

Study day for atomoxetine or placebo sessions:
After the paper work and ECG (if required), you would take the tablets as above, just once. You would then rest in a quiet area where you can read books or magazines, and watch television for up to 2 hours. This is a "cross over" study, which means that on different days you will receive atomoxetine and placebo. The order that you receive them will be randomised. In order to minimise placebo effects and/or experimenter bias from affecting your performance on the tests, we use different codes for each pill. This means that neither the experimenter nor you are aware of which pill contains the active drug. These codes will be revealed to the experimenter, if it is necessary to break the code early in the unlikely event of a significant side effect.

You will then undertake computerised tests designed to measure different aspects of your thinking and behaviour. These are designed to test your concentration, motor speed, attention and decision-making. They will involve looking at symbols on the screen and making responses. No computer literacy is required and there will be many rest breaks between the tests. The tests will take up to two hours.

We will take a blood sample at each session, each equivalent to 2 tsp (10 ml) before beginning the computerised tests. These samples will tell us the precise amount of Atomoxetine in your blood, which can vary from person to person. As for other ordinary blood tests, you may experience slight discomfort in the form of a sharp scratch.

What are the possible benefits and risks of participating?
Benefits: There will be no direct benefits to taking part in this study but you will have the pleasure of knowing that you have made a contribution to our understanding of brain illnesses, and the progress towards potential new treatments. We will reimburse travel expenses for you and a companion or escort if required.
Risks: The size of the dose of Atomoxetine we use is 40mg. This dose is that normally used to treat other patients in clinic but for this study it will only be given once. This means that the risk of side effects is low. However, as with all drugs, there is always some risk of side effects.

If side effects do occur, they are likely to be mild and short-lived. Any side effects of the drugs in this study would be experienced soon after taking the drugs, and we would expect these to go away within a few hours. A doctor will be available throughout the experiment just in case. You will be given a 24-hour contact number to call if you have any concerns after you take part in the study. Please note that you must not drive or operate heavy machinery later in the day after participation in the study.

The most common side effects for people taking regular daily doses of atomoxetine include constipation, dry mouth, nausea, decreased appetite, dizziness, trouble sleeping, sexual problems, menstrual cramps, allergic reactions and problems passing urine. It also causes a very small increase in pulse and blood pressure, and these will be monitored. The likelihood of you developing any of these symptoms from a single dose is small, and symptoms would improve within the day. As a precaution however, you should not drive or operate dangerous machinery later in the day after testing.

Where is the study run from?
The study is organised by Prof Rowe at the Cambridge University Department of Clinical neurosciences, including the Wolfson brain Imaging Centre (WBIC) and will be carried out here and at the Herchel Smith Building, Forvie Site Robinson Way, Cambridge Biomedical Campus, and the Addenbrooke's Clinical Research Centre NIHR/Wellcome Trust Clinical Research Facility, Cambridge Biomedical Campus, Hills Road (UK)

When is study starting and how long is it expected to run for?
March 2018 to April 2019

Who is funding the study?
Parkinson’s UK

Who is the main contact?
The main contact is Dr Claire O’Callaghan, claire.ocallaghan@sydney.edu.au
The principal investigator is Professor James Rowe, james.rowe@mrc-cbu.cam.ac.uk

Contact information

Type(s)
Public

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Type(s)

Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
049560

Protocol serial number
10/H0308/34

Study information

Scientific Title
Understanding cognition and action in Parkinson’s disease

Acronym
UCAPD

Study objectives
Cognitive deficits are common in Parkinson’s disease (PD). Unfortunately, treatment options for PD using dopaminergic drugs or deep-brain stimulation emphasise the motor disorder and may leave unchanged or even worsen key cognitive functions. There is therefore an urgent need to understand the non-dopaminergic deficits and non-motor symptoms in PD. It is premature to study the clinical efficacy of many drug or behavioural manipulations in PD. Conversely, advances in molecular biology are remote from an understanding of the complex behavioural problems associated with PD. Our approach is to study the important cognitive, structural and neuro-pharmacological features of PD at intermediate levels called ‘endophenotypes’. These endophenotypes include systems dominated by a handful of neurochemical modulators linked to a set of core cognitive systems. They characterise cognitive and behavioural patterns in PD that result from cell loss in frontal cortico-subcortical circuits and loss of neuromodulatory projections from the brainstem to cortex and striatum. These include noradrenaline (NA), serotonin (5HT) and acetylcholine (ACh) as well as dopamine (DA).

In PD there is an early and substantial loss of brain noradrenaline, due to degeneration in the locus coeruleus nucleus – the brain's main source of noradrenaline. In animal models and in patients with PD there is evidence that changes in noradrenaline transmission mediate impulsivity, decision making and response control, and that these abilities can be improved by medications enhancing noradrenaline. We therefore believe that the noradrenergic system is an attractive target for effective treatment of impulsivity and other cognitive changes in PD. The noradrenergic system can be safely and effectively enhanced by the drug atomoxetine, a drug that increases levels of noradrenaline in the brain by blocking the re-uptake action of noradrenaline at the synaptic cleft, i.e., prevents noradrenaline from being cleared from the spaces between neurons in the brain.

We hypothesise that atomoxetine will improve performance (relative to placebo) on the measures of response inhibition, learning and effort-based motivation that are assessed in our neuropsychological battery. Furthermore, we hypothesise that the extent of behavioural improvement that patients will show after atomoxetine will depend on their locus coeruleus integrity, with patients who have a more severely affected locus coeruleus showing greater improvements.

Ethics approval required
Old ethics approval format

Ethics approval(s)
28/03/2018, Health Research Authority (HRA) East of England - Cambridge Central Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 104 8388; cambridgecentral.rec@hra.nhs.uk), ref: 10/H0308/34

Study design
Double-blind placebo-controlled randomized crossover design

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Parkinson's disease

Interventions
The protocol includes several experiments investigating different drugs and patient groups, however for the purpose of ISRCTN registration we describe one experiment using the drug atomoxetine.

The participants enrolled in the study are people with Parkinson's disease. Each participant attends twice on separate days (at least 6 days apart) – once taking an oral preparation of the drug (atomoxetine 40 mg), and once taking an oral placebo. On each day of the assessment, the drug or placebo is taken in the morning. After a 2 hour wait time, a blood sample is taken in order to assess blood plasma levels for the drug taken. Participants then complete a neuropsychological test battery that takes approximately 2 hours. The battery includes computerised tasks that assess response inhibition, learning and motivation, and also measures of oculomotor function and heart rate. Each participant also has an MRI scan, on a separate day

within 3 months of the drug/placebo sessions; on that day they undergo the scan which takes 60 minutes, as well as standardised cognitive screening tests and a standardised assessment of clinical motor and non-motor symptoms.

Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome(s)
Measured 2 hours after taking drug/placebo:
1. Response inhibition measured using a stop-signal task and operationalised by the stop-signal reaction time (SSRT)
2. Learning performance measured using a computerised reinforcement learning task
3. Effort-based motivation measured using a computerised force production task
4. Physiological measures measured using a 3-channel electrocardiogram (ECG) to measure heart rate, and an eye tracker to measure oculomotor function and pupil diameter

Key secondary outcome(s))
1. Locus coeruleus integrity measured using magnetisation transfer weighted magnetic resonance imaging (MRI) scans. This scan will be part of a battery of scans including MRPAGE, resting BOLD-sensitive echo-planar imaging and T2. The scans are conducted on a separate day within 3 months of the drug/placebo sessions
2. General background data on the distribution and severity of clinical features, cognitive deficits and behavioural changes. Assessed using a battery of standardised questionnaires completed by the patient and an informant, and cognitive screening tests, completed within 2 weeks of the drug/placebo sessions. These measures are taken once and the battery includes:
2.1. Addenbrooke's Cognitive Examination - revised (ACE-r)
2.2. Mini-mental state examination (MMSE),
2.3. Montreal cognitive assessment (MoCA)
2.4. Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
2.5. Hospital Anxiety and Depression scale (HADS)
2.6. Cambridge Questionnaire for Apathy and Impulsivity (CAM-QUAIT)
2.7. Cambridge Behavioural Inventory (CBI)
2.8. Barratt Impulsiveness Scale (BIS-11)
2.9. Conners' Adult ADHD Rating Scale (CAARS)
2.10. Apathy Scale
2.11. Motivation and Energy Inventory (MEI)
2.12. REM sleep behaviour disorder screening questionnaire (RBDSQ)
3. Wellbeing, alertness and fatigue-related symptoms assessed using a Visual Analogue Scale completed before the drug/placebo and after the 2 hour wait time following drug administration, i.e. twice a day on study days

Completion date
15/04/2019

Eligibility

Key inclusion criteria
1. Idiopathic Parkinson’s disease
2. Hoehn and Yahr stage 1.5–3
3. Age 45 - 80 years
4. English speaking

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Sex
All

Total final enrolment
19

Key exclusion criteria
1. Dementia (MMSE 25 or less)
2. Clinically significant current depression
3. Contraindications to MRI
4. Contraindication to atomoxetine, including:
4.1 Ischemic heart disease or cardiac rhythm abnormalities
4.2 other significant non-ischemic cardiac disease
4.3 uncontrolled hypertension
4.4 adverse drug reactions to closely related drugs
4.5 major psychiatric disorders including mania or schizophrenia
4.6 epilepsy
4.7 warfarin/monoamine oxidase inhibitor
4.8 known hepatic or renal failure

Date of first enrolment
29/03/2018

Date of final enrolment
29/03/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Cambridge
Cambridge Centre for Frontotemporal Dementia and Related Disorders Department of Clinical Neurosciences
University of Cambridge
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Study participating centre
Addenbrooke's Clinical Research Centre NIHR/Wellcome Trust Clinical Research Facility & NIHR Clinical Investigation Ward
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Hills Road
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Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Charity

Funder Name
Parkinson's UK

Alternative Name(s)
Parkinson's Disease Society

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Anonymised datasets generated during and/or analysed during the current study will be available upon request from qualified academic researchers, for non-commercial purposes, following the publication of the principal reports from the study (expected by 2021). A material transfer agreement may be required, depending on the location of the receiving part and purposes of the sharing, to ensure adequate data confidentiality measures, limit third party sharing, commercial exploitation and de-anonymization of participants. Anonymised datasets generated and/or analysed during the current study during this study may be included in the subsequent results publication. The detailed procedures for data curation and sharing are in development and will be made available at a later date. In the meantime, researchers are asked to contact the study team at the above addresses.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version v3	09/01/2019	05/09/2020	No	No