ISRCTN48548553 https://doi.org/10.1186/ISRCTN48548553

A randomised trial to compare the effectiveness of two antidepressants (escitalopram, a selective serotonin re-uptake inhibitor, SSRI) and (nortriptyline, a tricyclic antidepressant, TCA) compared to placebo for the treatment of depression in patients with Parkinson's disease

Submission date
15/02/2019

Registration date
22/02/2019

Last Edited
27/04/2023

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Mental and Behavioural Disorders

[X] 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

Parkinson's disease is a progressive neurological disorder that leads to increasing disability and functional decline. Currently, psychological therapies are used to treat depression in Parkinson's disease but often antidepressant medications are also required. The most commonly used antidepressants in the UK are selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCA) which are used in millions of people to treat clinical depression. There is currently no conclusive evidence on the appropriate choice of antidepressants in Parkinson's disease. There is some trial evidence that SSRIs, such as escitalopram, can be used cautiously to treat depression in Parkinson's disease but cases of worsening of parkinsonism have been reported along with other side effects including an increase in falls. The TCA nortriptyline can have a beneficial effect on parkinsonian features, such as tremor in early Parkinson's disease, and some trial evidence has shown that TCAs are effective in the treatment of depressive symptoms in Parkinson's disease. However, TCAs are currently only recommended as a treatment for depression in Parkinson's disease if a patient was unable to tolerate the SSRI, due to their increased risk of side effects. Nortriptyline has also been suggested in laboratory studies to reduce the physical and mental changes in Parkinson's disease, but there is not yet any information from clinical trials to support this. If a patient wants to know more about depression associated with Parkinson's disease, they can talk to the doctor or nurse who is treating them. The aim of this study is to find out if the antidepressants escitalopram and nortriptyline are effective in the treatment of depression in patients with Parkinson's disease and their effect on slowing down the development of the movement symptoms associated with Parkinson's disease.

Who can participate?
Patients aged 18 years or abve with a confirmed diagnosis of Parkinson's disease and who have been experiencing depressive symptoms

What does the study involve?
Patients are randomly assigned to one of the two drugs (escitalopram or nortriptyline) or a placebo (dummy drug) and followed up for one year. Patients attend five trial appointments over a 12-month period. Throughout the trial they receive four deliveries in the post containing the trial treatment. They need to be at home when the medication is sent to them and the research staff at the hospital/neurology centre liaise with them beforehand to ensure that they are available for the delivery. Each time the trial medication is sent to them, they receive a phone call from a member of the research team to confirm that they have received it. At each trial visit, they are asked to complete a number of trial assessments including questionnaires. These questionnaires contain questions asking about depressive symptoms, anxiety and movement symptoms. There are also general questions asking about quality of life. Their doctor completes some questionnaires also asking about the patient's movement skills and their mental capabilities. If they have a carer, they are asked to complete two questionnaires which provide information on their quality of life and responsibilities.

What are the possible benefits and risks of participating?
If a patient is randomised to receive escitalopram or nortriptyline, this may help to treat their depression. They have a two in three chance of receiving either of the two antidepressants and a one in three chance of receiving placebo. Although there is no promise that this trial will benefit them personally, the results generated may help to improve the treatment options of people with depression in Parkinson's disease in the future. There are some medications that can cause serious side effects when taken with the trial medications. For patients' safety, they are aksed to tell the trial doctor about all medications they are taking before and during the trial. This includes other prescribed medicines, over the counter medicines, recreational drugs, herbal medicines or supplements. If they suffer any unpleasant effects or have any concerns regarding their health at any point during the trial, they will be told to tell their trial doctor or nurse. They may be asked to attend the clinic for an additional visit(s) for further examination or tests. The active trial drugs may pose unknown risks to a pregnant woman, an unborn baby, or a breastfeeding child. As such, pregnant women are not allowed to take part in this trial. Urine samples from female participants of child bearing potential will be tested at visits 1, 2, 3 and 4 to make sure they are not pregnant and patients will be advised to use adequate contraception for the duration of the trial. This trial includes an optional sub-study which requires a blood sample to be taken at visit 1. Taking blood can be uncomfortable, but rarely results in any serious problems. Reported side effects include feeling light-headed or faint, bruising and/or discomfort at the site of injection. All reasonable efforts are made to make this trial safe. Despite this, some risks might not be possible to predict. New information about the treatment being studied may become available while the trial is running. The patients will be told about any new findings that might affect whether they want to continue in the trial.

Where is the study run from?
University College London (UK)

When is the study starting and how long is it expected to run for?
June 2018 to April 2023

Who is funding the study?
National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (UK)

Who is the main contact?
Trial Manager, adept@ucl.ac.uk

Study website
https://www.ucl.ac.uk/comprehensive-clinical-trials-unit/research-projects/2023/jan/adept-pd

Contact information

Type(s)
Scientific

Contact name
Dr Helen Knowles

Contact details
Comprehensive Clinical Trials Unit at UCL
Institute of Clinical Trials and Methodology
UCL
Gower Street
London
United Kingdom
WC1E 6BT
+44 (0)203 108 7878
adept@ucl.ac.uk

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
39448; HTA 16/145/01

Study information

Scientific Title
A randomised placebo-controlled trial on the effectiveness of escitalopram and nortriptyline for depressive symptoms in Parkinson's disease.
Substudy on the effectiveness of nortriptyline to delay motor progression in Parkinson's disease with depressive symptoms compared to placebo.

Acronym
ADepT-PD

Study objectives
Based on the previous evidence from small trials, the hypothesis is that both SSRIs and TCAs are effective compared to placebo and the difference in efficacy between TCAs and SSRIs is likely to be small, but that the tolerability of SSRIs is higher in this population than that of TCA due to the rate of adverse effects.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 15/03/2019, London-Riverside REC (Level 3 Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT; +44 (0)207104 8204; nrescommittee.london-riverside@nhs.net) ref: 19/LO/0288

Study design
Multicentre double-blind randomized placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Depression in patients with Parkinson's disease

Interventions
Current interventions as of 27/04/2023:

Method of randomisation: Stratified randomisation will be performed with strata defined by site and depression severity (BDI-II 0-19/20-63).

Patients will be randomly assigned to one of the two drugs or a placebo and followed up for one year.

Escitalopram target dose:
1. 65 years and under: starting dose 1 tablet daily (5 mg). Thereafter, dosage will be increased by one tablet per day, at two-weekly intervals, to a maximum of four tablets (20 mg) per day.
2. Over 65 years and/or those with hepatic impairment: starting dose 1 tablet daily (5 mg). Thereafter, dosage will be increased by one tablet per day, at two-weekly intervals, to a maximum of two tablets (10 mg) per day.

Nortriptyline target dose:
1. 65 years and under: starting dose 1 tablet daily (25 mg). Thereafter, dosage will be increased by one tablet per day, at two-weekly intervals, to a maximum of four tablets (100 mg) per day.
2. Over 65 years and/or those with hepatic impairment: starting dose 1 tablet daily (25 mg). Thereafter, the escitalopram dosage will be increased by one tablet per day, at two-weekly intervals, to a maximum of two tablets (50 mg) per day.

Total duration of treatment (all arms): All patients will receive trial medication for between 54 and 58 weeks.

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Previous interventions:

Method of randomisation: Stratified randomisation will be performed with strata defined by site and depression severity (BDI-II 0-19/20-63).

Patients will be randomly assigned to one of the two drugs or a placebo and followed up for one year.

Escitalopram target dose:
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Nortriptyline target dose:
1. 65 years and under: starting dose 1 tablet daily (25 mg). Thereafter, dosage will be increased by one tablet per day, at two-weekly intervals, to a maximum of four tablets (100 mg) per day.
2. Over 65 years and those with hepatic impairment: starting dose 1 tablet daily (25 mg). Thereafter, the escitalopram dosage will be increased by one tablet per day, at two-weekly intervals, to a maximum of two tablets (50 mg) per day.

Total duration of treatment (all arms): All patients will receive trial medication for between 53 and 56 weeks.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Escitalopram, nortriptyline

Primary outcome measure
Depressive symptoms measured using the Beck Depression Inventory (BDI-II) at 8 weeks of treatment

Secondary outcome measures

Measured at 8, 26 and 52 weeks of treatment:
Patient-reported outcomes:
1. Level of depression measured using the Becks Depression Inventory (BDI-II) at weeks 26 and 52
2. Level of depression measured using the Patient Health Questionnaire (PHQ9)
3. Number of participants experiencing side effects (adverse reactions) on the Modified Toronto Side Effects Scale and reporting of other adverse events
4. Anxiety symptoms measured using the Parkinson Anxiety Scale
5. Quality of life measured using the EQ-5D-5L questionnaire
6. Capability measured using the ICECAP-O questionnaire
7. Health and social care resource use measured using the modified Client Service Receipt Inventory (CSRI)
8. Time spent by paid carers measured using a modified version of the iMTA Valuation of Informal Carers Questionnaire (iVICQ) (asked alongside the CSRI)
9. Changes in concomitant medication

Clinician and patient-reported outcomes:
1. Motor and non-motor experiences measured using the MDS-UPDRS69 Part I and II, and motor examination and motor complications measured using the MDS-UPDRS Part III and IV (including a recording of the participant's movements)

Clinician-reported outcomes:
1. Cognitive function measured using the Montreal Cognitive Assessment (MoCA)
2. Overall clinical effectiveness measured using the Global Clinical Impression scale (CGI) - change in health question
3. Levodopa-equivalence dose
4. Number of drop-outs

Carer-reported outcomes:
The trial does not require that the participants have a carer, however, if a participant does have a carer, the carer will be asked if they agree to complete the following questionnaires:
1. Carer's quality of life measured using the EQ-5D-5L63-64 and Carers Quality of Life Questionnaire for Parkinsonism
2. Impact on informal carers measured using a modified version of the iVICQ68 (asked alongside the CSRI)

Overall study start date
01/06/2018

Completion date
30/04/2023

Eligibility

Key inclusion criteria
Current inclusion criteria as of 27/04/2023:

1. Patients with a diagnosis of idiopathic PD, based on a history and neurological exam performed by the enrolling investigator with presence of at least two of the three cardinal signs of PD: rigidity, bradykinesia, and rest tremor with no evidence of diagnostic alternatives.
2. Aged 18 years old or above

3. Fulfilling operationally defined subsyndromal depression (presence of two or more depressive symptoms at threshold or subthreshold levels, at least one of which had to include depressed mood or anhedonia or diagnostic (DSM-V) criteria for a depressive disorder (i.e. major depressive disorder or persistent depressive disorder)).
4. Beck Depression Inventory-II (BDI-II) score ≥14.
5. Written informed consent provided.
6. Treatment with antiparkinsonian medication is optimised or stable for at least 4 weeks before date of randomisation and there are no plans to change up to primary endpoint (8 weeks).

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Previous inclusion criteria:

1. Patients with a diagnosis of idiopathic PD, based on a history and neurological exam performed by the enrolling investigator with presence of at least two of the three cardinal signs of PD: rigidity, bradykinesia, and rest tremor with no evidence of diagnostic alternatives
2. Aged 18 to 85 years
3. Fulfilling diagnostic (DSM-V) criteria for a depressive disorder (i.e., major depressive disorder or persistent depressive disorder) or operationally defined subsyndromal depression (presence of two or more depressive symptoms at threshold or subthreshold levels, at least one of which has to include depressed mood or anhedonia
4. Beck Depression Inventory-II (BDI-II) score > = 14 5. Written informed consent provided

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
408

Total final enrolment
52

Key exclusion criteria
Current exclusion criteria as of 27/04/2023:

1. Women who are pregnant, breastfeeding or of childbearing potential without effective contraception (hormonal or barrier method of birth control; or abstinence). Periodic abstinence (e.g.calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Patients who do not have sufficient understanding of the English language to be or are not able to understand the Patient Information Sheet or the self-completed questionnaires or patients who are unable to communicate answers to the self-rating questionnaires.

3. Patients with Montreal Cognitive Assessment (MoCA) score <16 or without capacity to consent.
4. Treatment with an antidepressant within 4 weeks of enrolment (except for a small dose of amitriptyline up to 30 mg for indications other than depression).
5. Patients with known severe liver failure.
6. Absolute contraindications to escitalopram or nortriptyline. These include:
a. Patients with known QT-interval prolongation57 or congenital long QT syndrome.
b. Recent myocardial infarction (<3 months), any degree of heart block or other cardiac arrhythmias precluding treatment with nortriptyline or escitalopram according to clinical judgement.
7. Medications contraindicated on nortriptyline or escitalopram. These include:
a. Non-selective and selective irreversible monoamine oxidase inhibitors (MAOIs) within 14 days. However, the antiparkinsonian selective reversible MAO-B inhibitors rasagiline, selegiline and safinamide are not contraindicated.
b. Concomitant QT prolonging drugs, including domperidone, apomorphine at high doses (single dose or hourly rate of >6mg), certain neuroleptics (not quetiapine or clozapine), quinine, class IA and III antiarrhythmics (amiodarone, dronedarone and disopryamide), the antihistamines astemizole, mizolastine, the antimicrobial agents sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarian treatment), and some antiretrovirals.
8. Patients indicating active suicidal ideation or intent on the BDI-II item 9 and who, after clinical review of risk using the standardised Suicide Risk Management Protocol, need to be referred for immediate treatment.
9. Participation in another clinical trial of an investigational medicinal product or device within the last 30 days of randomisation.
10. Any clinical condition which in the opinion/ clinical judgement of the investigator would make the patient unsuitable for the trial due to safety concerns.

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Previous exclusion criteria:

1. Women who are pregnant, breastfeeding or of childbearing potential without effective contraception (hormonal or barrier method of birth control; or abstinence)
2. Patients who do not have sufficient understanding of the English language to be able to read and understand the self-completed questionnaires or patients who are unable to communicate answers to the self-rating questionnaires
3. Patients with Montreal Cognitive Assessment (MoCA) score < 16 or without capacity to consent
4. Treatment with an antidepressant within 4 weeks of enrolment (except for a small dose of amitriptyline up to 50 mg for indications other than depression)
5. Absolute contraindications to escitalopram or nortriptyline. These include: a. Patients with known QT-interval prolongation or congenital long QT syndrome. b. Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias
6. Medications contraindicated on nortriptyline or escitalopram. These include: a. Non-selective and selective irreversible monoamine oxidase inhibitors (MAOIs) within 14 days. However, the antiparkinsonian selective reversible MAO-B inhibitors rasagiline, selegiline and safinamide are not contraindicated b. Concomitant QT prolonging drugs, including domperidone, apomorphine at high doses (single dose or hourly rate of > 6mg), certain neuroleptics (not quetiapine or clozapine), quinine, class IA and III antiarrhythmics (amiodarone, dronedarone and disopryamide), the antihistamines astemizole, mizolastine, the antimicrobial agents sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarian treatment),and some antiretrovirals
7. Patients indicating active suicidal ideation or intent on the BDI-II item 9 and who, after clinical

review of risk using the standardised Suicide Risk Management Protocol, need to be referred for immediate treatment
8. Treatment with antiparkinsonian medication should be optimized and stable within 4 weeks of receiving the trial medication and with no plans to change up to primary endpoint (8 weeks)
9. Enrolment in another clinical trial of an investigational medicinal product or device within the last 30 days

Date of first enrolment
30/11/2020

Date of final enrolment
09/11/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Royal Free London NHS Foundation Trust
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
Lewisham and Greenwich NHS Trust
University Hospital Lewisham
Lewisham High Street
London
United Kingdom
SE13 6LH

Study participating centre
Luton and Dunstable University Hospital
Lewsey Road
Luton
United Kingdom
LU4 0DZ

Study participating centre
Northumbria Healthcare NHS Foundation Trust
North Tyneside General Hospital
Rake Lane
North Shields
United Kingdom
NE29 8NH

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Christchurch Hospital, University Hospitals Dorset
Christchurch Hospital
Fairmile Road
Christchurch
United Kingdom
BH23 2JX

Study participating centre
St Peters Hospital
Guildford Road
Chertsey
United Kingdom
KT16 0PZ

Study participating centre
Royal Cornwall Hospitals NHS Trust
Royal Cornwall Hospital
Treliske
Truro
United Kingdom
TR1 3LJ

Study participating centre

Cornwall Partnership NHS Foundation Trust
Carew House
Beacon Technology Park
Dunmere Road
Bodmin
United Kingdom
PL31 2QN

Study participating centre
NIHR Newcastle Clinical Ageing Research Unit (CARU)
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
National Hospital for Neurology & Neurosurgery
Queen Square
London
United Kingdom
WC1N 3BG

Study participating centre
Yeovil District Hospital NHS Foundation Trust
Higher Kingston
Yeovil
United Kingdom
BA21 4AT

Study participating centre
Addenbrookes
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre

Charing Cross Hospital
Fulham Palace Road
London
United Kingdom
W6 8RF

Study participating centre
Livewell Southwest
Local Care Centre
200 Mount Gould Road
Plymouth
United Kingdom
PL4 7PY

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Sponsor information

Organisation
University College London

Sponsor details
Gower Street
Bloomsbury
London
England
United Kingdom
WC1E 6BT
+44 (0)203 108 7878
adpet@ucl.ac.uk

Sponsor type
University/education

Website
http://www.ucl.ac.uk/

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 16/145/01

Results and Publications

Publication and dissemination plan
Current publication and dissemination plan, as of 27/04/2023:

Planned publication in peer-reviewed journal and to funder

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Previous publication and dissemination plan:

The protocol is currently being reviewed by the HRA and REC. The protocol will be published in an open access journal after approval by the REC.

The trial will be registered with international trials databases such as ClinicalTrials.gov, and reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement for the results (http://www.consortstatement.org/). The protocol will be aimed to be published in an open access journal. The findings from this trial will be disseminated widely, primarily through publication in international academic journals and conferences. The findings will be publicised through media offices of the host institution UCL and Parkinson's UK, the large PD Patient Support organization in the UK and the NIHR itself, and will directly provide the results to those developing NICE's Public Health Guidance. Given that this will be the largest trial in this field, it is anticipated that the lack of sufficient evidence outlined in the currently available meta-analyses on the effect of the studies interventions, the results will influence national as well as international guidelines on the management of depression in PD.

Intention to publish date
30/04/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Anette Schrag (adept@ucl.ac.uk), after formal discussion/application to the Trial Steering Committee (TSC), consent will be obtained from participants, and only anonymised data will be available.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		12/12/2022	27/04/2023	Yes	No
HRA research summary			28/06/2023	No	No