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Dopamine and memory consolidation

Submission date	Recruitment status	[X] Prospectively registered
10/08/2015	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
19/08/2015	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
24/04/2023	Mental and Behavioural Disorders	

Plain English summary of protocol

Current plain English summary as of 06/07/2020:
Background and study aims
Alzheimer's disease (AD) is the most common type of dementia, which causes problems with memory, thinking and behaviour (cognitive function). AD often develops slowly and the symptoms can be confused with other illnesses. One of these is mild cognitive impairment (MCI) which also causes problems with memory and thinking. People living with MCI have difficulties with certain aspects of daily life, but they are not as severe or noticeable to others as someone with dementia. A person living with MCI is more likely to develop dementia such as AD later in life.
Dopamine is a chemical messenger which carries signals throughout the brain and the body (neurotransmitters). It has been suggested that this neurotransmitter is important for cognitive function, and low levels could play a role in the development of MCI and AD. This study aims to find out whether giving a person medication which increases the activity of dopamine in the brain overnight, will improve memory storage during a good night's sleep. In this preliminary study we test the effect of levodopa in healthy older people and in future we aim to test people with MCI

Who can participate?
Healthy people aged 65 years or older

What does the study involve?
All participants visit the testing centre on three separate occasions. At each visit, the participants are be asked to learn a list of words. They are then given a single dose of medication. The participants are divided into groups who will receive the medications in different orders. On one visit, they are given a single dose of the medication co-beneldopa and on another visit they are given a placebo (dummy pill). The participants then spend the night and have their sleep monitored. After a full night's sleep, they take a memory recall test of the list of words they learnt at the beginning of the visit. All participants also have a structural magnetic resonance brain scan (MRI) taken, and 24 of the participants will also have a functional imaging (fMRI) scan taken. The memory test is then repeated over the phone 3 days and 5 days later. There is a 7-day gap between visits so that the medication taken on one visit would not interfere with the medication taken on the next visit.

What are the possible benefits and risks of participating?
There are no direct benefits to taking part in this study and every care has been taken to minimise risks. With careful safety screening, MRI is a safe procedure and accidents are extremely rare. EEG recording of sleep is also safe and non-invasive. The drugs in this trial are widely used and generally safe. However, some people experience side effects, such as nausea, and so study volunteers will be given medication to prevent this.

Where is the study run from?
Clinical Research and Imaging Centre Bristol (UK)

When is the study starting and how long is it expected to run for?
September 2015 to September 2019

Who is funding the study?
1. Medical Research Council (UK)
2. Alzheimer's BRACE Bristol (UK)
3. Wellcome Trust (UK)

Who is the main contact?
Dr Elizabeth Coulthard (Scientific)
elizabeth.coulthard@bristol.ac.uk
Ms Hanna Isotalus (Public)
hanna.isotalus@nbt.nhs.uk

Previous plain English summary as of 20/04/2018:

Background and study aims
Alzheimer’s disease (AD) is the most common type of dementia, which causes problems with memory, thinking and behaviour (cognitive function). AD often develops slowly and the symptoms can be confused with other illnesses. One of these is mild cognitive impairment (MCI) which also causes problems with memory and thinking. People living with MCI have difficulties with certain aspects of daily life, but they are not as severe or noticeable to others as someone with dementia. A person living with MCI is more likely to develop dementia such as AD later in life.
Dopamine is a chemical messenger which carries signals throughout the brain and the body (neurotransmitters). It has been suggested that this neurotransmitter is important for cognitive function, and low levels could play a role in the development of MCI and AD. This study aims to find out whether giving a person medication which increases the activity of dopamine in the brain overnight, will improve memory storage during a good night's sleep.

Who can participate?
Seniors with a diagnosis of MCI or mild AD, and age-matched healthy controls

What does the study involve?
All participants visit the testing centre on three separate occasions. At each visit, the participants are be asked to learn a list of words. They are then given a single dose of medication. The participants are divided into groups who will receive the medications in different orders. On one visit, they are given a single dose of the medication co-beneldopa and on another visit they are given a placebo (dummy pill). The participants then spend the night and have their sleep monitored. After a full night’s sleep, they take a memory recall test of the list of words they learnt at the beginning of the visit. All participants also have a structural magnetic resonance brain scan (MRI) taken, and 24 of the healthy participants will also have a functional

imaging (fMRI) scan taken. The memory test is then repeated over the phone 3 days and 5 days later. There is a 7-day gap between visits so that the medication taken on one visit would not interfere with the medication taken on the next visit.

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There are no direct benefits to taking part in this study and every care has been taken to minimise risks. With careful safety screening, MRI is a safe procedure and accidents are extremely rare. EEG recording of sleep is also safe and non-invasive. The drugs in this trial are widely used and generally safe. However, some people experience side effects, such as nausea, and so study volunteers will be given medication to prevent this.

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Previous plain English summary:

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Alzheimer’s disease (AD) is the most common type of dementia, which causes problems with memory, thinking and behaviour (cognitive function). AD often develops slowly and the symptoms can be confused with other illnesses. One of these is mild cognitive impairment (MCI) which also causes problems with memory and thinking. People suffering from MCI have difficulties with certain aspects of daily life, but they are not as severe or noticeable to others as someone with dementia. It is thought that a person suffering from MCI is more likely to develop dementia such as AD later in life.
Dopamine is a chemical messenger which carries signals throughout the brain and the body (neurotransmitters). It has been suggested that this neurotransmitter is important for cognitive function, and low levels could play a key role in the development of MCI and AD. This study aims to find out whether giving a person medication which increases the activity of dopamine in the brain overnight, will improve memory storage during a good night's sleep.

Who can participate?
Seniors with a diagnosis of MCI or mild AD, and age-matched healthy controls

What does the study involve?
All participants visit the testing centre on four separate occasions. At each visit, the participants are be asked to learn a list of words. They are then given a single dose of medication. The participants are divided into groups who will receive the medications in different orders. On one visit, they are given a single dose of the medication co-beneldopa, on another visit they are

given ropinirole and on another visit they are given a placebo (dummy pill). The participants then spend the night and have their sleep monitored. After a full night's sleep, they take a memory recall test of the list of words they learnt at the beginning of the visit. All participants also have a structural magnetic resonance brain scan (MRI) taken, and 24 of the healthy participants will also have a functional imaging (fMRI) scan taken. This test is then repeated over the phone 3 days and 5 days later. There is a 7-day gap between visits so that the medication taken on one visit would not interfere with the medication taken on the next visit.

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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2015-002027-26

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
6

Study information

Scientific Title
Targeting dopamine to treat impaired memory consolidation in neurodegenerative disease

Acronym
DOPAMIND

Study objectives
Current study hypothesis as of 06/07/2020:
When dopaminergic drugs, as opposed to placebo, are administered overnight, memory of episodic, associative and reward information will be improved 12 hours, 3 and 5 days later in older healthy adults (65+ years).

Previous study hypothesis as of 20/04/2018:
1. When dopaminergic drugs, as opposed to placebo, are administered overnight, memory of episodic, associative and reward information will be improved 12 hours, 3 and 5 days later in older healthy adults (65+ years).
2. When dopaminergic drugs, as opposed to placebo, are administered overnight, memory of episodic, associative and reward information will be improved 12 hours, 3 and 5 days later in those living with MCI or AD.

Original study hypothesis:
1. When dopaminergic drugs, as opposed to placebo, are administered overnight, memory of episodic, associative and reward information will be improved 12 hours, 3 and 5 days later in older healthy adults (65+ years).

2. When dopaminergic drugs, as opposed to placebo, are administered overnight, memory of episodic, associative and reward information will be improved 12 hours, 3 and 5 days later in those living with MCI or AD.
3. Both patients and healthy adults will experience a greater improvement in memory on cobeneldopa than on ropinirole, due to its ability to increase D1 receptor activity.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South West - Central Bristol Ethics Committee, 13/04/2016, REC ref: 16/SW/0028

Study design
Single-centre placebo-controlled double-blind randomised cross-over study with single doses

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Healthy ageing, amnesic mild cognitive impairment and mild to moderate Alzheimer's dementia.

Interventions
Current interventions as of 06/07/2020:
A cohort of healthy control participants undergo block randomisation into groups, who will receive each treatment in a different order. Participants will visit the testing facility on three occasions. At each visit they will receive either a single dose of co-beneldopa 200mg or a single dose of placebo, with at least a 7-day wash-over period between dosing.
These groups are as follows:
1. 1st visit placebo, 2nd visit co-beneldopa
2. 1st visit co-beneldopa, 2nd visit placebo
Each testing visit entails a learning phase, followed by a single-dose of a drug, an early recall and a late recall after a full night’s sleep.
After dosing, the participants will stay at the research facility overnight and have their sleep monitored using sleep electroencephalography (EEG), to examine the relationship between memory performance, dopamine and sleep architecture. All participants will have a structural magnetic resonance brain scan (MRI) taken, and a subset of 24 healthy controls will also undergo functional imaging (fMRI). A recall of the verbal learning task will be performed over the phone after 3 and 5 days.

Previous interventions as of 20/04/2018:
Three groups of patients (healthy control, Alzheimer's disease and Mild Cognitive Impairment) undergo block randomisation into further groups, who will receive each treatment in a different order. Participants will visit the testing facility on three occasions. At each visit they will receive either a single dose of co-beneldopa 200mg or a single dose of placebo, with at least a 7-day wash-over period between dosing.
These groups are as follows:
1. 1st visit placebo, 2nd visit co-beneldopa
2. 1st visit co-beneldopa, 2nd visit placebo
Each testing visit entails a learning phase, followed by a single-dose of a drug, an early recall and a late recall after a full night's sleep.
After dosing, the participants will stay at the research facility overnight and have their sleep monitored using sleep electroencephalography (EEG), to examine the relationship between memory performance, dopamine and sleep architecture. All participants will have a structural magnetic resonance brain scan (MRI) taken, and a subset of 24 healthy controls will also undergo functional imaging (fMRI). A recall of the verbal learning task will be performed over the phone after 3 and 5 days.

Previous interventions:
Three groups of patients (healthy control, Alzheimer's disease and Mild Cognitive Impairment) undergo block randomisation into further groups, who will receive each treatment in a different order. Participants will visit the testing facility on four occasions. At each visit they will receive either a single dose of ropinirole 8mg, a single dose of co-beneldopa 200mg or a single dose of placebo, with at least a 7-day wash-over period between dosing.
These groups are as follows:
1. 1st visit ropinirole, 2nd visit co-beneldopa, 3rd visit placebo
2. 1st visit ropinirole, 2nd visit placebo, 3rd visit co-beneldopa
3. 1st visit placebo, 2nd visit co-beneldopa, 3rd visit ropinirole
4. 1st visit placebo, 2nd visit ropinirole, 3rd visit co-beneldopa
5. 1st visit co-beneldopa, 2nd visit placebo, 3rd visit ropinirole
6. 1st visit co-beneldopa, 2nd visit ropinirole, 3rd visit placebo
Each testing visit entails a learning phase, followed by a single-dose of a drug, an early recall and a late recall after a full night's sleep.
After dosing, the participants will stay at the research facility overnight and have their sleep monitored using sleep electroencephalography (EEG), to examine the relationship between memory performance, dopamine and sleep architecture. All participants will have a structural magnetic resonance brain scan (MRI) taken, and a subset of 24 healthy controls will also undergo functional imaging (fMRI). A recall of the verbal learning task will be performed over the phone after 3 and 5 days.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Current drug names as of 20/04/2018: Co-beneldopa (200 mg dose) Original drug names: 1. Ropinirole (8 mg dose) 2. Co-beneldopa (200 mg dose)

Primary outcome measure

The change in behavioural performance on memory and learning tasks (number of words recalled) after 12 hours and after 3 and 5 days after medication.

Secondary outcome measures
1. Time spent (in minutes) in different sleep stages as measured from EEG of sleep during the night following administration
2. Hippocampal subfield volume and shape to be measured using MRI and fMRI. Structural MRI is taken at baseline, fMRI is taken between 1 and 3 hours following drug administration
3. White matter tractography as measured by diffusion weighted imaging
4. Functional correlativity (Pearson's r) between VTA BOLD and hippocampus BOLD signals
5. Sensory preconditioning/reinforcement learning task the ratio of choices of rewarded actions compared to non-rewarded
6. Attention and motor learning tasks raw reaction times measured at baseline, 30 minutes after dosing, 12 hours after dosing

Overall study start date
01/09/2015

Completion date
01/09/2019

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 06/07/2020:
1. Native or fluent English speakers (highly proficient in English language)
2. Normal or corrected to normal vision
3. Aged 65 years or older
4. Participants must have mental capacity to consent, and score above 11/30 in the Montreal Cognitive Assessment test

Previous participant inclusion criteria:
1. Native or fluent English speakers (highly proficient in English language)
2. Normal or corrected to normal vision
3. Aged 65 years or older (may recruit younger patients if age-matched healthy control can be found)
4. Diagnosis of Mild cognitive impairment (MCI) or mild Alzheimer's Disease (AD)
5. Participants must have mental capacity to consent, and score above 11/30 in the Montreal Cognitive Assessment test

Participant type(s)
Mixed

Age group
Senior

Sex
Both

Target number of participants

90

Total final enrolment
35

Key exclusion criteria
Current exclusion criteria as of 20/04/2018:
1. The participants must not have:
1. 1. Clinically significant neurological or psychiatric diagnoses, other than MCI or mild AD for the patient group. This will be assessed by self-report and questionnaires during the screening visit
1.2. Known posterior cortical atrophy (mainly relevant for MCI and AD, who will have had a brain scan as a part of the diagnostic procedure)
1.3. Clinically significant sleep problems in the past year
1.4. An undiagnosed skin lesion. Participants will be asked about this.
1.5. Known sensitivity to levodopa, ropinirole, benserazide, or domperidone
1.6. Known lactose intolerance, galactosemia or glucose/galactose malabsorption
1.7. Known galactose intolerance
1.8. Known Lapp lactase deficiency
1.9. Diagnosis of Huntington's Chorea
1.10. Intention tremor. This will be screened for by a trained investigator
1.11. Known prolactin-releasing pituitary tumour (prolactinoma)
1.12 Diagnosis of glaucoma
1.13 A history of, or current, malignant melanoma
1.14 Diagnosed diabetes
1.15 Known osteomalacia
1.16 Severe endocrine, hepatic, renal, pulmonary, or cardiac disorder
1.17 Diagnosed electrolyte disturbances
1.18 Known peptic ulcers
1.19 History of a heart-attack or prolongation of cardiac conduction intervals, or any other cardiac problems as taking domperidone increases risk of said problems. An ECG will be taken at the screening visit and heart-rate and blood pressure will be monitored before and after drug administration, as specified elsewhere in this protocol.
1.20. Current cancer treatment
1.21. End stage renal disease or severe renal impairment
1.22. Diagnosed hepatic impairment
1.23 Pregnant women and women of childbearing potential not using adequate contraception will
be excluded in line with the Madopar SmPC
2. The participant must not be taking:
2.1 Dopaminergic medications
2.2 Noradrenergic, serotonergic, or anticholinergic medications, except if the participant has been on stable treatment (at least 3 months) for pain or mood disorders
2.3 Monoamine oxidase inhibitors (MAO-I), except if selective MAO-A or MAO-B inhibitors are given. MAO-A and MAO-B inhibitors given together are equivalent to non-selective MAO-inhibition and therefore volunteers taking both MAO-A and MAO-B will not be included in this study
2.4. Cholinesterase inhibitors, except if the participant has been on stable treatment (at least 3 months)
2.5. Antihypertensive (blood pressure) drugs containing reserpine
2.6. Ferrous sulphate on the day of testing
2.7. Opioids or sympathomimetics (e.g. amphetamines, epinephrine/adrenaline)

2.8. Diazepam
2.9 Ketoconazole, erythromycin or CYP3A4 inhibitors (e.g. fluoconazole, voriconazole, clarithromycin, amiodarone, telithryomycin)
2.10. Antibiotics
2.11. Hormone replacement therapy
2.12. Anti-fungal agents (pentamidine)
2.13. Anti-malarial agents
2.14. Gastro-intestinal medicines
2.15. Antihistaminics
2.16. AIDS/HIV medications
2.17. If a participant takes antacids or antisecretory agents they should not be taken at the same time as domperidone (but these participants can be included if the medication can be taken at a different time)
2.18. Any medication known to interfere with co-beneldopa or domperidone

Original exclusion criteria:
1. The participants must not have:
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1.2. Known posterior cortical atrophy (mainly relevant for MCI and AD, who will have had a brain scan as a part of the diagnostic procedure)
1.3. Clinically significant sleep problems in the past year
1.4. An undiagnosed skin lesion. Participants will be asked about this.
1.5. Known sensitivity to levodopa, ropinirole, benserazide, or domperidone
1.6. Known lactose intolerance, galactosemia or glucose/galactose malabsorption
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2.18. Any medication known to interfere with co-beneldopa, ropinirole or domperidone

Date of first enrolment
01/11/2015

Date of final enrolment
01/09/2018

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Clinical Research and Imaging Centre Bristol
University of Bristol
60 St Michael's Hill
Bristol
United Kingdom
BS2 8DX

Sponsor information

Organisation
University of Bristol

Sponsor details
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Sponsor type
University/education

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ROR
https://ror.org/0524sp257

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Alzheimer's BRACE Bristol

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The results of this trial will be published in a scientific journal and written as a part of a PhD thesis. They will also be presented at national and international scientific meetings and conferences.

2020 results in preprint in https://doi.org/10.1101/2020.05.23.112375 (added 30/11/2020)

Intention to publish date
01/12/2019

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		05/04/2023	24/04/2023	Yes	No
HRA research summary			28/06/2023	No	No