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A trial to investigate the effect on overall health and functioning in patients with Lewy body dementia of memantine as an add-on treatment to a cholinesterase inhibitor

Submission date
30/04/2022

Recruitment status
Recruiting

Registration date
12/07/2022

Overall study status
Ongoing

Last Edited
18/11/2025

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
Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are related complex illnesses with a wide range of distressing symptoms. People with DLB/PDD have worse quality of life, more complex symptoms, higher care costs, and are more sensitive to medications than people with Alzheimer's disease (AD).
Acetylcholinesterase Inhibitors (AChEI) are commonly used medicines that can help people with DLB/PDD by improving day to day functioning and thinking abilities. Another drug which might help is memantine, used to treat moderate to severe confusion in AD. It may help to improve memory, awareness and the ability to perform daily functions; however, it is not clear if adding memantine to AChEI is beneficial for people with DLB/PDD.

The aim of this trial is to find out if adding memantine to AChEI improves overall health and functioning for people with DLB or PDD.
COBALT is a double-blind, placebo-controlled, randomised trial to assess the clinical and cost-effectiveness of memantine compared to placebo in patients on an AChEI with DLB (COBALT-DLB) and PDD (COBALT-PDD). There are two separate COBALT trials being carried out using the same protocol, one in the UK and one in Australia. We plan to recruit a total of 372 patients and their caregivers/informants. The UK trial will recruit 300 participants from 30 sites and the Australian trial will recruit 72 participants from up to 5 sites. UK and Australian data will be combined for analysis.

Who can participate?
Patients aged 55 years or older with DLB or PDD, and their caregivers/informants.

What does the study involve?
DLB/PDD patients aged ≥55 years with a Mini Mental State Examination score of ≥8, on a stable dose of AChEI will be randomised 1:1 to memantine or placebo for 52 weeks. Both trials are identical in procedure and conduct, with the only variation being the disease group.

Participants and their caregiver/informant will complete assessments at baseline, 26 weeks (primary, secondary and exploratory outcomes) and 52 weeks (secondary and exploratory outcomes). During these visits assessments will be completed by the patient and their caregiver /informant.

What are the possible benefits and risks of participating?
Benefits:
The COBALT trial may help to improve treatment for people with DLB and PDD. The patients who participate in the trial may gain significant satisfaction from contributing and the regular contact from the local trial team.
Risks:
Memantine is well tolerated in patients with moderate to severe dementia in Alzheimer's Disease, with adverse events (AEs) reported in 10% of patients (comparable to placebo). The most frequently occurring adverse reactions are dizziness, headache, constipation, somnolence, and hypertension. Patients will undergo a titration phase in the first 4 weeks of their participation to assess how well they tolerate the IMP.
At some visits the questionnaires and memory testing may take 1-2 hours. Participants may find the questions tiring, tedious or embarrassing. Participants may choose not to answer any specific questions or do any test at any time.
We will ensure there are adequate rest breaks, however participants or their caregiver /informant can also request a break at any time. If the patient/caregiver requests an extended break, the assessments can be paused but must be resumed within 7 days of the initial visit.
Where is the study run from?
UK Trial - Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust (UK)
Australian Trial - The University of Melbourne (UoM)

When is the study starting and how long is it expected to run for?
March 2022 to March 2025

Who is funding the study?
NIHR Health Technology Assessment programme in the UK and National Health Medical Research Council in Australia.

Who is the main contact?
Sarah Dunn (UK), cobalt.study@ncl.ac.uk
Lesley Vidaurre (Australia), vidaurre.l@wehi.edu.au

Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-003232-88

Integrated Research Application System (IRAS)
1004660

Protocol serial number
RES-20-041, IRAS 1004660, ERM ID 79783, CPMS 51602

Study information

Scientific Title
COmBining memantine And cholinesterase inhibitors in Lewy body dementia Treatment trial

Acronym
COBALT

Study objectives
What is the clinical and cost effectiveness of memantine compared to placebo in patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) who are being treated with an acetylcholinesterase inhibitor (donepezil, rivastigmine or galantamine)?
Clinical effectiveness is determined using a global outcome scale - the Clinical Global Impression of Change (CGIC), 6 months after recruitment.
Cost effectiveness will be measured using health economic indicators, in particular the Client Services Receipt Inventory which has been adapted for use specifically for the COBALT trial and looks at the participant's use of health and social care services.

The secondary and exploratory objectives include determining whether active treatment with memantine vs. placebo leads to changes in:
1. Carer-based impression of global changes (using an adapted CGIC)
2. Cognitive function
3. Neuropsychiatric symptom frequency and severity
4. Quality of life and function for the patient
5. Quality of life for the care-giver
6. Long-term changes in global outcomes

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 04/07/2022, East of England - Essex Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; +44 (0)2071048227; essex.rec@hra.nhs.uk), ref: 22/EE/0075

2. approved 24/05/2023, Royal Melbourne Hospital (Grattan Street, Parkville, 3050, Australia; +61 3 9342 8530; research@mh.org.au), ref: 2023.031

Study design
Interventional double-blind randomized parallel group placebo-controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD)

Interventions
Memantine will be the Investigational Medicinal Product (IMP) for the COBALT trials. Memantine is currently licensed for the treatment of moderate to severe dementia in Alzheimer's disease and is used off-licence in the UK for treatment of other dementias including DLB and PDD.
IMP: Memantine 10mg tablets and Memantine 5mg tablets (Oral capsules).
Placebo: Matched placebo tablets for memantine 5mg and 10 mg tablets will be manufactured and classed as an IMP for this trial (Oral capsules).

All participants will receive an initial 4-week titration pack with clear instructions stated in the participant diary (part 1) dose instructions table. This table must be completed by the local trial team and the participant must be in receipt of the diary prior to starting the IMP. The 4-week titration schedule will start at 5mg daily in a single dose, taken in the morning. Thereafter, the dose will be increased by 5mg every week. The target dose will be 20mg/day, taken in the morning but titration will be based on tolerability and response.
Potentially eligible patients will attend a screening visit during which consent will be obtained prior to any eligibility checks and the trial eligibility confirmation will be performed. This will include review of Liver and kidney function tests within the preceding 6 months. If no test results are available within this timeframe, a blood sample will be required to carry out these tests. A Mini Mental State Examination (MMSE) will be completed with the patient and a clinical diagnostic worksheet will be completed to confirm the patient's diagnosis (Dementia with Lewy Bodies or Parkinson's Disease Dementia). The patients will also be required to have a caregiver /informant in order to be eligible for the trial. The patient's caregiver/informant should be a person that is in regular contact with the patient, who knows the patient well and is able to attend the trial follow-up visits as required. The caregiver/informant will complete assessments relating to the patient and themselves during the scheduled trial visits. The caregiver/informant should be identified during the screening process and is required to consent to take part in the COBALT trial.
Once the patient has been consented and confirmed eligible, they will be randomised as a participant in either the COBALT – DLB or COBALT – PDD module of the trial, depending on their diagnosis confirmed at screening. For each trial module, a central, secure, web-based randomisation system with concealed allocation (Sealed Envelope – UK; REDCap – Aus)) will assign participants to active or placebo treatment in a 1:1 ratio. All participants, their caregiver /informants and site staff will be blinded to the participants treatment allocation, meaning that they will not know if the participant is receiving active or placebo treatment.
The baseline assessments can be carried out once the participant has been consented, screened and randomised. This can occur at the same visit or can be scheduled for another day, within 14 days of the consent and screening visit. At baseline the primary, secondary, and exploratory outcome assessments will be conducted. IMP will be dispensed, along with the participant diary to record any adverse events, missed trial medication, visits to health care professionals and changes to concomitant medications. The participants and their caregiver/informant will also be given a participant safety card that includes information relating to their participation and emergency contact numbers for the trial team. Participants will be instructed to carry the card at

all times and present it to any healthcare professional that they see during their COBALT trial participation.
Following the participants initial baseline visit a number of follow up visits are required.
Visit 5 (week 26) - These visits may occur at the local trial site, in the participant's home. The primary, secondary and exploratory outcome assessments will be conducted per protocol section 7.4.2. IMP will be dispensed, IMP adherence will be checked along with any side effects /Adverse Events and changes to the participant's concomitant medications.
Visit 7 (week 52)/Early Withdrawal - These visits may occur at the local trial site, in the participant's home. Secondary and exploratory outcomes will be conducted per protocol section 7.4.3. IMP adherence will be checked along with any side effects/Adverse Events and changes to the participant's concomitant medications.
Visit 2 (week 3), Visit 3 (week 8), Visit 4 (week 14) and Visit 6 (week 38) - These visits may occur at the local trial site, in the participant's home or by telephone/video call. IMP adherence will be checked along with any side effects/Adverse Events and changes to the participant's concomitant medications per protocol section 7.4.4. At visit 4 and visit 6 IMP will be dispensed to ensure a continued supply for the participant.
A Resolution Call will be made to participants at week 56 (Visit 8) to document any adverse events they have experienced following the Visit 7 (week 52)/Early Withdrawal visit per protocol section 7.4.5.
Participants are given the option to consent to a long-term follow up 12 months after the end of their participation in the trial. This can either be by review of the medical records or by speaking to someone from the local or central trial team, depending on what the participant agrees to. The purpose of this additional follow-up is to understand the long-term outcomes for patients with DLB and PDD following treatment with memantine.
At selected Australian trial sites, participant consent will be obtained to collect and store approximately 60mL of blood for future research including for example biomarker development, genomics, transciptomics. Blood may be collected at up to 3 timepoints throughout the trial i.e. baseline, week 26 and week 52.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Memantine hydrochloride neuraxpharm 5 mg film-coated tablets, memantine Torrent 10 mg film-coated tablets

Primary outcome(s)
Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC) scale at 26 and 52 weeks post baseline

Key secondary outcome(s))
COBALT-DLB and COBALT-PDD
at baseline, 26 and 52 weeks:
1. Caregiver/Informant Impression of Change (C/I-CGIC)
2. Montreal Cognitive Assessment (MoCA)
3. Neuropsychiatric Inventory Plus (NPI+)
4. Quality of life: EuroQol EQ-5D 5 Level (EQ-5D-5L) - patient
5. Quality of life: EQ-5D-5L – proxy

6. Hospital and Anxiety Depression Scale (HADS)
7. Disability Assessment for Dementia (DAD)
8. Impact of memantine on motor function: The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (MDS UPDRS-III
9. Epworth Sleepiness Scale (ESS)
10. Client Service Receipt Inventory (CSRI)
11. Zarit Burden Interview (ZBI) - Caregiver/informant
12. WHO Quality of Life - BREF

Completion date
31/03/2027

Eligibility

Key inclusion criteria
Current inclusion criteria as of 21/12/2023:
1. Patients with a diagnosis or clinical features consistent with established consensus criteria for probable DLB or probable PDD
2. Aged ≥55 years
3. MMSE score ≥8. Evidence of mild, moderate, or moderate to severe cognitive impairment on similar global cognitive scales previously completed by their clinical care team (e.g., Addenbrooke's Cognitive Examination, Mini-Addenbrooke's Cognitive Examination, Montreal Cognitive Assessment) can be used to pre-screen the patient, prior to approach.
4. Receiving a stable dose of AChEI for ≥12 weeks prior to baseline, with no expected plans for dose adjustment during the trial period; dose adjustment will be allowed during the trial, if clinically indicated, following discussion with PI and, if required, the central trial team
5. If receiving any antiparkinsonian treatment, antidepressants, anxiolytics, antipsychotics, or other drugs with significant psychotropic effects then dose must be stable for a minimum of 4 weeks prior to enrolment with no expected plans for dose adjustment during the trial period. Dose adjustment will be allowed during the trial if clinically indicated and will be documented. If a change in medication with psychotropic effects is required, this decision can be made by the treating clinician (e.g., starting an antidepressant in clinic) without consultation with the CI. In some instances, the clinician may feel it is appropriate/relevant to discuss this with the PI prior to prescribing, for example, if the clinician feels that the medication change may have an impact on the trial and/or trial medication. Any changes should however be documented in the patient's concomitant medications electronic Case Report Form (eCRF).
6. Patients who lack capacity will be required to have a personal/professional nominated representative who is able to give informed consent on the patient's behalf
7. Females must be postmenopausal and not receiving IVF treatment or must have undergone permanent sterilisation. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
8. Patients with sufficient knowledge of the English language or support to understand the Patient Information Sheet and complete the trial assessments

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Previous inclusion criteria:
1. Patients with a diagnosis or clinical features consistent with established consensus criteria for probable DLB or probable PDD.
2. Aged ≥50.

3. MMSE score ≥ 8.*
4. Receiving a stable dose of AChEI for ≥12 weeks prior to baseline, with no expected plans for dose adjustment during the trial period; dose adjustment will be allowed during the trial, if clinically indicated, following discussion with PI and, if required, the central trial team.
5. If receiving any antiparkinsonian treatment, antidepressants, anxiolytics, antipsychotics, or other drugs with significant psychotropic effects then dose must be stable for a minimum of 4 weeks prior to enrolment with no expected plans for dose adjustment during the trial period. †
6. Patients who lack capacity will be required to have a personal/professional nominated representative who is able to give informed consent on the patient's behalf.
7. 7. Females must be postmenopausal and not receiving IVF treatment or must have undergone permanent sterilisation††
8. Patients with sufficient knowledge of the English language or support to understand the Patient Information Sheet and complete the trial assessments
*Evidence of mild, moderate, or moderate to severe cognitive impairment on similar global cognitive scales previously completed by their clinical care team (e.g., Addenbrooke's Cognitive Examination, Mini-Addenbrooke's Cognitive Examination, Montreal Cognitive Assessment) can be used to pre-screen the patient, prior to approach.
†If a change in medication with psychotropic effects is required, this decision can be made by the treating clinician (e.g., starting an antidepressant in clinic) without consultation with the CI. In some instances, the clinician may feel it is appropriate/relevant to discuss this with the PI prior to prescribing, for example, if the clinician feels that the medication change may have an impact on the trial and/or trial medication. Any changes should however be documented in the patient's concomitant medications electronic Case Report Form (eCRF).
††Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
55 years

Upper age limit
99 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Atypical clinical features or course suggestive of an alternative dementia diagnosis.
2. Any clinically relevant concomitant disease that will affect ability to participate in the trial

including, but not limited to, chronic renal disease stage 5, history of acute or chronic pancreatitis, epilepsy or former history of convulsions, patients with recent myocardial infarction (within last 6 months), uncompensated congestive heart failure (NYHA III-IV), or uncontrolled hypertension.
3. Patients with severe hepatic impairment based on known history and/or significant abnormalities identified in blood liver function tests (for example, levels in liver function tests that are 2-3 times higher than the upper limit of normal), which in the judgement of the local PI would exclude the patient from the trial.*
4. Patients taking memantine, amantadine, ketamine, or dextromethorphan.
5. Any neurological or major psychiatric diagnosis that may be contributing to cognitive impairment above and beyond that caused by the patients DLB or PDD.
6. Renally impaired patients with eGFR <35 mL/min/1.73m².†
7. Currently taking part in another clinical trial that would interfere with the outcomes of the COBALT trial.
8. If in the opinion of the investigator, the patient would be unable to comply with the trial procedures or has difficulty taking oral medications.
9. Patients without a reliable caregiver/informant.
*LFTs should be repeated if they were not carried out at screening and were abnormal in the last 6 months and/or, in the judgement of the local PI, are clinically relevant to check before deciding trial entry.
†U&Es should be repeated if they were not carried out at screening and were abnormal in the last 6 months and/or, in the judgement of the local PI, are clinically relevant to check before deciding trial entry. For example, a borderline eGRF <45 mL/min/1.73m².

Date of first enrolment
24/11/2022

Date of final enrolment
31/08/2026

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Australia

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne

England
NE7 7DN

Study participating centre
South London and Maudsley NHS Foundation Trust
Bethlem Royal Hospital
Monks Orchard Road
Beckenham
England
BR3 3BX

Study participating centre
Cambridgeshire and Peterborough NHS Foundation Trust
Elizabeth House,
Fulbourn Hospital
Fulbourn
Cambridge
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CB21 5EF

Study participating centre
Essex Partnership University NHS Foundation Trust
The Lodge
Lodge Approach
Runwell
Wickford
England
SS11 7XX

Study participating centre
Norfolk and Suffolk NHS Foundation Trust
Hellesdon Hospital
Drayton High Road
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NR6 5BE

Study participating centre
Southern Health NHS Foundation Trust
Tatchbury Mount Hospital
Calmore

Southampton
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SO40 2RZ

Study participating centre
Queen Elizabeth University Hospital
1345 Govan Road
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Scotland
G51 4TF

Study participating centre
Sussex Partnership NHS Foundation Trust
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BN13 3EP

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EX2 5AF

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BS10 5NB

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Sheffield Health & Social Care NHS Foundation Trust
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Sheffield
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S10 3TH

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Tees, Esk and Wear Valleys NHS Foundation Trust
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Study participating centre

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University College London Hospitals NHS Foundation Trust
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Study participating centre
Kent and Medway NHS and Social Care Partnership Trust
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Study participating centre
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Study participating centre
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Study participating centre

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Sponsor information

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ROR
https://ror.org/01ajv0n48

Organisation
University of Melbourne

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
National Health and Medical Research Council

Alternative Name(s)
National Health and Medical Research Council, Australian Government, NHMRC National Health and Medical Research Council, NHMRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Australia

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request. We will provide a contact in due course but this is likely to be the Chief Investigator, Professor John – Paul Taylor.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	version 4.0	01/03/2023	27/03/2024	No	Yes
Protocol file	version 3.0	29/06/2022	17/10/2022	No	No
Protocol file	version 6.0	11/07/2024	07/11/2024	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes