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Study of mirtazapine for agitation in dementia

Submission date
13/07/2016

Recruitment status
No longer recruiting

Registration date
28/07/2016

Overall study status
Completed

Last Edited
05/08/2025

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Dementia is a common condition in the aging population. People with dementia have difficulties with mental processes such as memory, language, reasoning and identifying people and objects, which become progressively worst over time. There are a range of different types of dementia, but the most common is Alzheimer's disease (AD). Agitation and aggression are common in people who suffer from dementia and can cause problems for the patients, families and the people caring for them. In many cases, agitation is persistent, with many still showing symptoms after six months. There are medicines available to treat agitation, but it is not clear which treatments work best for people with dementia. Current treatments include antipsychotic medication, but these only have limited positive effects and can cause harm. Non-drug treatments are recommended in the first instance, but there is a need for medicines to be available, if non-drug treatments fail. The aim of this study is to investigate the effectiveness of mirtazapine (a type of antidepressant), in the management of agitation in people with dementia.

Who can participate?
Adults with dementia who are also displaying agitated behaviours, and their carers (family or paid carer)

What does the study involve?
Participants are randomly allocated to one of two groups. The study is designed so that the participant, their carer, their doctors and the research team do not know which they are taking until the end. Those in the first group are given mirtazapine, those in the second group are given a placebo (dummy pill). All tablets are made in such a way that they look the same, although it is possible to find out which medicine is being taken, in the event of a medical emergency. In both groups, participants are asked to take one tablet for the first two weeks of treatment in the trial, two tablets in the next two weeks and three tablets for the remaining eight weeks of the treatment period (unless there are concerns about side effects resulting from them taking the medication). A blood and ECG (test to check the heart rhythm) test are taken before medication is given and after treatment stops, at 12 weeks. Participants will continue to receive care from their doctors and other health and social services in the usual way whilst they are taking part in the study, and are carefully monitored throughout. Participants and their carers complete a number of questionnaires at the start of the study and then after 6 and 12 weeks to measure agitation and quality of life. There is a long term follow up phone call, six months and one year after trial medication is first taken.

What are the possible benefits and risks of participating?
Benefits can't be promised, but participation may lead to improved treatments for people with similar symptoms in future. It is however possible that participants may benefit from lower levels of agitation as a result of taking the medication in this study, and improved quality of life for them and their carers. Disadvantages include that the trial will take up time. Blood tests are being taken for participant safety but may cause some discomfort and/or inconvenience. Mirtazapine does have side effects but most are mild and resolve on their own. These may include: stomach upset, weight gain, feeling drowsy, dizzy, headaches and more rarely a rash and blood problems. A full summary is provided to participants and side effects are carefully monitored by the trial team.

Where is the study run from?
NHS trusts across the UK

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

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
1. Miss Juliet High (public)
symbad@uea.ac.uk
2. Prof. Sube Banerjee (scientific)
sube.banerjee@plymouth.ac.uk

Contact information

Type(s)
Public

Contact name
Miss Juliet High

Contact details
Norwich Clinical Trials Unit
Norwich Medical School
University of East Anglia
Norwich Research Park
Norwich
United Kingdom
NR4 7TJ
+44 1603 591708
symbad@uea.ac.uk

Type(s)
Scientific

Contact name
Prof Sube Banerjee

Contact details
Executive Dean & Professor of Dementia
University of Plymouth
Faculty of Health
403 Rolle Building
Plymouth
United Kingdom
PL4 8AA
+44 01752 586740
sube.banerjee@plymouth.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2015-003410-25

ClinicalTrials.gov (NCT)
NCT03031184

Protocol serial number
30474

Study information

Scientific Title
A pragmatic, multi-centre, double-blind, placebo controlled randomised trial to assess the safety, clinical and cost effectiveness of mirtazapine in patients with Alzheimer's Disease (AD) and agitated behaviours

Study objectives
Current study hypothesis:
The aim of this study is to assess the safety, clinical and cost effectiveness of mirtazapine in the management of agitation and/or aggression in people with dementia.

Previous study hypothesis:
The aim of this study is to assess the safety, clinical and cost effectiveness of mirtazapine or carbamazepine in the management of agitation and/or aggression in people with dementia.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Committee: South Central – Hampshire A, 04/11/2015, ref: 15/SC/0606

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Agitation and/or aggression in people with dementia

Interventions
Current interventions as of 28/01/2019:
Patients will be randomised in a 1:1 ratio to mirtazapine or placebo, stratified by study region and independent living using permuted block randomisation via a web-based system.
Mirtazapine is a generic 15mg tablet, over encapsulated. IMP and placebo will be identically encapsulated to produce capsules.
Mirtazapine group: Participants receive 15mg starting dose increasing to 30mg after 2 weeks and up to 45 mg in total.
Placebo group: Participants receive 1 capsule starting dose increasing to 2 capsules after 2 weeks and up to 3 capsules in total.
IMP or placebo will be taken for 12 weeks in total. Patients/their carers will be contacted by phone 4 weeks after they stop taking IMP to ask how they are feeling and record any adverse events (AEs). Long term follow up will be at 26 and 52 weeks.

Previous interventions:
Patients will be randomised in a 1:1:1 ratio to mirtazapine, carbamazepine or placebo, stratified by study region and independent living using permuted block randomisation via a web-based system.
Mirtazapine is a generic 15mg tablet, over encapsulated. Carbamazepine is specifically Tegretol Extended Release 100mg tablet, over encapsulated. IMP and placebo will be identically encapsulated (15mg tablets for mirtazapine and 100mg tablets for carbamazepine) to produce capsules.
Mirtazapine group: Participants receive 15mg starting dose increasing to 30mg after 2 weeks and up to 45 mg in total.
Carbamazepine group: Participants receive 100mg starting dose increasing to 200mg after 2 weeks and up to 300mg in total.
Placebo group: Participants receive 1 capsule starting dose increasing to 2 capsules after 2 weeks and up to 3 capsules in total.
IMP or placebo will be taken for 12 weeks in total. Patients/their carers will be contacted by phone 4 weeks after they stop taking IMP to ask how they are feeling and record any adverse events (AEs). Long term follow up will be at 26 and 52 weeks.

Intervention Type
Drug

Phase
Phase III

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

Primary outcome(s)
Agitation is measured using the Cohen Mansfield Agitation Inventory (CMAI) long version, at baseline and 12 weeks.

Key secondary outcome(s))
1. Cost effectiveness is assessed using a modified Client Service Receipt Inventory (CSRI), alongside information from DEMQOL and EQ-5D-5L interviews at baseline, 6 and 12 weeks
2. Agitation is measured using the CMAI score at 6 weeks (in addition to the primary outcome measure, as a secondary outcome measure)
3. Patient and carer quality of life is assessed via the Zarit carer burden, GHQ-12 and EQ-5D questionnaires at baseline, 6 and 12 weeks
4. Safety is assessed by looking at adverse events and adherence at 6 and 12 weeks. Adverse events are measured by face to face visits, follow up phone calls, review of medical records, notification by other health care professionals, blood and ECG test results and collection of a diary card which is completed by the patient/carer. Adherence is assessed by tablet counts, follow up phone calls and review of a diary card which is completed by the patient/carer, at week 2, 4, 6 and 12.

Long term follow up takes place at 26 and 52 weeks and is assessed via a phone call:
1. Agitation is measured using CMAI
2. Institutionalisation is assessed using a study specific questionnaire
3. Mortality is measured using a study specific questionnaire
4. Clinical management is assessed using a study specific questionnaire

Completion date
30/06/2020

Eligibility

Key inclusion criteria
1. Aged 18 years and over
2. Clinical diagnosis of probable or possible Alzheimer's Disease using National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria
3. A diagnosis of co-existing agitated behaviours
4. Evidence that the agitated behaviours have not responded to management according to the AS/DH algorithm
5. If receiving cholinesterase inhibitors or memantine, must be on a stable dose (defined as three months on current dose)
6. A Cohen Mansfield Agitation Inventory score of 45 or greater
7. Written informed consent to enter and be randomised into the trial or consultee agreement for those without capacity
8. Availability of a suitable informant (consenting identifiable family carer or paid carer) to provide information on carer-completed outcome measures and who consents to take part in the trial

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
247

Key exclusion criteria
Current exclusion criteria as of 28/01/2019:
1. Current treatment with antidepressants (including monoamine oxidase inhibitors (MAOIs)), anticonvulsants, antipsychotics. Patients must have completed treatment with these medications at least two weeks before trial drug administration
2. Contraindications to the administration of mirtazapine as per its current SmPCs
3. Patients with atrioventricular block, a history of bone marrow depression or history of hepatic porphyrias
4. Cases too critical for randomisation (ie where there is a suicide risk or where the patient presents a risk of harm to others)
5. Female subjects under the age of 55 of childbearing potential, defined as follows: postmenopausal females who have not had at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhoea with serum FSH>40mIU/ml or females who have not had a hysterectomy or bilateral oophorectomy at least 6 weeks prior to enrolment

Previous exclusion criteria:
1. Current treatment with antidepressants (including monoamine oxidase inhibitors (MAOIs)), anticonvulsants, antipsychotics. Patients must have completed treatment with these medications at least two weeks before trial drug administration
2. Contraindications to the administration of carbamazepine and mirtazapine as per their current SmPCs
3. Patients with atrioventricular block, a history of bone marrow depression or history of hepatic porphyrias
4. Cases too critical for randomisation (ie where there is a suicide risk or where the patient presents a risk of harm to others)
5. Female subjects under the age of 55 of childbearing potential, defined as follows: postmenopausal females who have not had at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhoea with serum FSH>40mIU/ml or females who have not had a hysterectomy or bilateral oophorectomy at least 6 weeks prior to enrolment

Date of first enrolment
01/09/2016

Date of final enrolment
29/02/2020

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Sussex Partnership NHS Foundation Trust
Grove House
Southview Road
Crowborough
United Kingdom
TN6 1HB

Study participating centre
Norfolk and Waveney Mental Health NHS Foundation Trust
Hellesdon Hospital
Drayton High Road
Norwich
United Kingdom
NR6 5BE

Study participating centre
Gateshead Health Foundation Trust
Clinical Trials Office
Cheviot View
Queen Elizabeth Hospital
Queen Elizabeth Avenue
Sheriff Hill
Gateshead
United Kingdom
NE9 6SX

Study participating centre
Manchester Mental Health and Social Care Trust
Greater Manchester Central Manchester University Hospitals NHS Foundation Trust
West Road
Off North Road (Between Children's and Adults A&E Departments)
Manchester
United Kingdom
M13 9WL

Study participating centre
Camden and Islington NHS Foundation Trust and Barnet, Enfield and Haringey Mental Health Trust
St. Pancras Hospital

4 St. Pancras Way
London
United Kingdom
NW1 3TH

Study participating centre
Birmingham and Solihull Mental Health NHS Foundation Trust
Barberry Centre
25 Vincent Drive
Edgbaston
United Kingdom
B15 2FG

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
Guys and St Thomas Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
Surrey and Borders Partnership NHS Foundation Trust
Research and Development Department
Abraham Cowley Unit
St Peter’s Hospital
Guildford Road
Chertsey
United Kingdom
KT16 OPZ

Study participating centre
Barnet Enfield & Haringey Mental Health NHS Trust
St. Ann's Hospital
London
United Kingdom
N15 3TH

Study participating centre
Bradford District Care Foundation Trust
Lynfield Mount Hospital

Bradford
United Kingdom
BD9 6DP

Study participating centre
2gether Gloucestershire NHS Foundation Trust
Cheltenham
United Kingdom
GL53 9DZ

Sponsor information

Organisation
University of Sussex

ROR
https://ror.org/00ayhx656

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during the current study will be available upon request from Prof Sube Banerjee (sube.banerjee@plymouth.ac.uk) once the trial follow-up and analyses are completed. The likely date for this is October 2022.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		23/10/2021	26/10/2021	Yes	No
Results article		01/10/2023	06/11/2023	Yes	No
Abstract results		03/12/2022	05/08/2025	No	No
HRA research summary			28/06/2023	No	No
Protocol file	version 2.0	01/08/2018	31/03/2023	No	No