

Study of mirtazapine for agitation in dementia

Submission date 13/07/2016	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 28/07/2016	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 06/11/2023	Condition category Mental and Behavioural Disorders	<input type="checkbox"/> 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**EudraCT/CTIS number**

2015-003410-25

IRAS number**ClinicalTrials.gov number**

NCT03031184

Secondary identifying numbers

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

Secondary study design

Randomised controlled trial

Study setting(s)

Not specified

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

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 measure

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

Secondary outcome measures

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/carers. Adherence is assessed by tablet counts, follow up phone calls and review of a diary card which is completed by the patient/carers, 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

Overall study start date

01/12/2015

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

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

Planned Sample Size: 262; UK Sample Size: 262

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

England

United Kingdom

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

Sponsor details

C/O Nigel Knight, Head of Contracts and IP

Falmer House

Falmer

Brighton

England

United Kingdom

BN1 9QF

Sponsor type

Hospital/treatment centre

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

Publication and dissemination plan

1. The dissemination plan will include facilitating the translation of findings of the research into practice. The plan will be developed during the trial, but the audience will include clinicians, people with dementia and their carers, other health care professionals and policy makers. All participants will have the option to request a copy of the results, all outputs will be tailored in style and content to the intended audience.
2. The data will be published in high impact, peer reviewed journals and open access to the papers will be enabled. Minimum publications will include: the trial protocol, a primary paper for publication of the results, a secondary clinical outcome paper, secondary economic evaluation paper, HTA publication of the final report and publication of the long term follow up data.
3. There will also be presentations at conferences and seminars, both locally, nationally and internationally.

Intention to publish date

01/09/2021

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	version 2.0	23/10/2021	26/10/2021	Yes	No
Protocol file		01/08/2018	31/03/2023	No	No
HRA research summary			28/06/2023	No	No
Results article		01/10/2023	06/11/2023	Yes	No