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Antiglucocorticoid augmentation of antiDepressants in Depression: the ADD study

Submission date
27/10/2009

Recruitment status
No longer recruiting

Registration date
21/12/2009

Overall study status
Completed

Last Edited
02/11/2017

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims.
The aim of this study is to test a drug called metyrapone in patients with moderate to severe depression, as an add-on to current antidepressant treatment. Depression is a common disorder, affecting approximately 10% of the population. The effects can be long-lasting and may recur frequently. Depression has a negative impact on people's quality of life, not only for those who are diagnosed with the condition, but also for their carers. Research has shown that many people with depression also produce more cortisol than is usual. This may stop antidepressant drugs from working properly. The researchers would like to learn whether giving a drug named metyrapone, in addition to a standard antidepressant for a short space of time (three weeks), produces benefits that are meaningful to patients with depression. Previous research on the drug metyrapone has shown that it can block the production of the stress hormone cortisol produced in the body. The ADD study is also designed to see whether any postive effects of metyrapone last beyond the three weeks during which it is given.

Who can participate?
Patients living in the community and visiting clinics on a regular basis for monitoring of their moderate to severe depression

What does the study involve?
Participants are randomly allocated to be given either metyrapone or an identical-looking capsule that does not contain any active medicine (a placebo or dummy pill). They continue with their current antidepressant treatment at the same time. Participating in the study involves taking two capsules twice a day, every day for three weeks. The capsules are taken at 12 noon and at bedtime, with milk or after a meal. As this study is 'blinded' it is not possible to tell, until the end of the study, which treatment group patients have been in. Not knowing whether patients are taking metyrapone or placebo does not affect the treatment given at the end of the study. Once recruited into the study, medication is posted to the patient's address of their choice. A prescription is written which is faxed to the Pharmacy based at the Northumberland, Tyne & Wear NHS Foundation Trust, where responsibility lies for dispensing of study medication. Local research teams check participants' progress throughout this treatment period, and for a further 21 weeks afterwards. Mood, general health and social function are assessed. This enables the research teams to understand how patients are feeling during the study and

ascertains whether any beneficial effects last over time. Blood samples are taken for routine tests, as well as saliva samples to measure stress hormone levels. With additional permission, a sample is taken for genetic (DNA) analysis. A number of genes have been identified that might be involved in depression. A comparison is made to compare the variations in these genes with the stress hormone level and other tests carried out with how well the drug treatment works to try and understand the reasons for why people vary in their response to treatment. The results are also compared with people who are not depressed (healthy volunteers) to better understand what happens in depression. A sub-group of patients are invited to take part in extra sub-studies investigating the stress system in depression and how metyrapone affects this. Patients may choose to participate in these extra tests which include: computer tests of brain processes such as memory and attention; brain imaging (Magnetic Resonance Imaging; MRI); and electrical recording of brain activity (electroencephalogram; EEG). The aim is to understand more about how stress can cause depression, how treatments may be improved, and if a prediction can be made whether a patient will respond before giving a particular treatment. A separate group of healthy volunteers are also invited to participate in the sub-studies but do not receive metyrapone or placebo treatments.

What are the possible benefits and risks of participating?
Metyrapone may improve the symptoms of depression. Participants who take part in studies generally feel better more than participants who don't. This may be down to the more frequent follow-up of patients compared to routine clinical practice. There may be no direct benefit, but participants will help in finding out whether metyrapone is useful in depressed patients and help doctors understand more about the role of stress hormones in this disorder. There is no promise that the study will help current participants, but it may help future patients. There may be side effects of metyrapone; these will be explained in detail by the medical team and included in the patient information sheet. There is a small risk of bruising or discomfort at the injection site when blood samples taken.

Where is the study run from?
Newcastle University Institute of Neuroscience (UK)

When is the study starting and how long is it expected to run for?
February 2011 to June 2013

Who is funding the study?
National Institute for Health Research Efficacy and Mechanism Evaluation (NIHR EME) (UK)

Who is the main contact?
Professor Nicol Ferrier
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Contact information

Type(s)
Scientific

Contact name
Prof Ian Nicol Ferrier

Contact details

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Additional identifiers

Clinical Trials Information System (CTIS)
2009-015165-31

ClinicalTrials.gov (NCT)
NCT01375920

Protocol serial number
EME 08/43/39

Study information

Scientific Title
Antiglucocorticoid augmentation of antiDepressants in Depression: a double-blind randomised placebo-controlled parallel group trial

Acronym
ADD

Study objectives
That a three week course of metyrapone (versus placebo) augmentation of antidepressants in depressed patients who have failed to respond to at least two courses of antidepressants, in primary care and psychiatric outpatient clinics in the UK will be lead to a reduction in symptoms of depression.

Link to EME project website: http://www.eme.ac.uk/projectfiles/084339info.pdf

Ethics approval required
Old ethics approval format

Ethics approval(s)
Sunderland Research Ethics Committee, 22/04/2010, ref: 10/H0904/9

Study design
Double-blind randomised placebo-controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Major depression

Interventions
Metyrapone 500 mg twice a day or twice daily placebo for 21 days in addition to the patient's current ongoing psychotropic medication which will remain stable throughout the trial.

Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome(s)
Change in clinical symptoms of depression from 0 to +5 weeks (i.e. two weeks after end of treatment), assessed by the Montgomery-Asberg Depression Research Scale (MADRS)

Key secondary outcome(s))
Current secondary outcome measures as of 28/06/2013:
1. Mood as measured by the MADRS, YMRS and BDI at time 0, +3, +5, +8, +16, +24 weeks
2. Anxiety as measured by the CAS and STAI at time 0, +3, +5, +8, +16, +24 weeks
3. Quality of life, assessed using the EQ-5D at weeks 0, +3, +5, +8, +16, +24
4. Tolerability assessed using the TSES and self-report at weeks 0, +3, +5, +8 (additional self-report at weeks +1, +2 and +4)
5. Suicide risk assessed at weeks 0, +1, +3, +5, +8, +16, +24
6. Hypothalamic-Pituitary-Adrenal (HPA) axis function assessed by salivary cortisol awakening response (CAR) and sample at 11 pm at weeks 0, +3 and +5
7. Safety assessments including blood pressure, urea and electrolytes and plasma cortisol levels at weeks -2, +1 and +5

Previous secondary outcome measures until 28/06/2013:
1. Secondary outcomes related to mood will be the MADRS measured at time 0, +3, +5, +8, +16, +24 weeks relative to baseline (protocol amendement approved 15/08/2011)
2. Quality of lfe, assessed using the EQ-5D at weeks 0, +3, +5, +8, +16, +24
3. Cortisol awakening response (CAR) from salivary samples at weeks 0, +3 and +5

Previous secondary outcome measures until 05/02/2013:
1. Secondary outcomes related to mood will be the MADRS measured at time +3, +8, +16 and + 24 weeks relative to baseline

Previous secondary outcome measures until 16/06/2011:
2. Quality of life, assessed using the EQ-5D at weeks 0, +3 and +5

Completion date
30/06/2013

Eligibility

Key inclusion criteria
Current inclusion criteria as of 05/02/2013:
1. Males and females aged 18-65 years
2. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) confirmed diagnosis of major depression
3. Severity - Patients must have a Hamilton Depression Rating Scale (HDRS17) score of 18 or greater, consistent with a moderate to severe episode. The stability of the patients' clinical state will also be confirmed with a 2 week baseline lead in period (week -2 to 0). A repeat HDRS17 score at time 0 is required to be 18 or greater.
4. Treatment refractoriness - assessed using the Massachusetts General Hospital (MGH) staging method. This defines minimum effective doses of all currently available antidepressants and an "adequate trial" as being for at least 6 weeks. For the trial to be considered as a "failure" it must have been considered by the clinical team to have been ineffective rather than the drug not taken or not tolerated. For inclusion, patients will have failed to have responded to at least their second trial of an antidepressant. This equates to a minimum score of 2 on MGH staging. The maximum MGH score for inclusion in the study will be 10.
5. At trial entry, patients must be taking monotherapy or combination antidepressant therapy that includes a serotonergic drug (a selective serotonin reuptake inhibitor [SSRI], a tertiary amine tricyclic, venlafaxine, duloxetine or mirtazepine). They must not be on noradrenergic antidepressant monotherapy eg. lofepramine, imipramine or reboxitene. At the point of randomisation, patients must have been on their current antidepressant medication, at the current dose, for a minimum of four weeks (protocol amendment approved 05/03/2012).

Previous inclusion criteria until 05/02/2013:
5. At trial entry, patients must be taking monotherapy or combination antidepressant therapy that includes a serotonergic drug (a selective serotonin reuptake inhibitor [SSRI], a tertiary amine tricyclic, venlafaxine, duloxetine or mirtazepine). (Added 16/06/2011: They must not be on noradrenergic antidepressant monotherapy eg. lofepramine, imipramine or reboxitene).

Previous inclusion criteria until 16/06/2011:
1. Males and females aged 18 - 70 years
3. Severity - Patients must have a Hamilton Depression Rating Scale (HDRS17) score of 18 or greater, consistent with a moderate to severe episode. The stability of the patients' clinical state will also be confirmed with a 2 week baseline lead in period (week 2 to 0). A repeat HDRS17 score at time 0 is required to be 18 or greater.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
65 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 05/02/2013:
1. Any other DSM IV Axis I disorder other than an anxiety disorder unless the depressive episode is considered to be secondary to the anxiety disorder, confirmed using the Structured Clinical interview for DSM (SCID) (protocol amendment approved 15/08/20111)
2. Physical co-morbidity which would render the use of metyrapone inappropriate, including untreated hypothyroidism, disorders of steroid production, cardiac failure, angina, myocardial infarction within the last 3 years, renal failure
3. Pregnancy - determined by history and if indicated, urine pregnancy test
4. Mothers who are breastfeeding
5. Use of concomitant medication that would interfere in a pharmacodynamic or pharmacokinetic manner with metyrapone
6. Dependence on alcohol or other drug in the past 12 months and/or current harmful use of alcohol or other drug
7. Recently having taken part in another research study that could interfere with the results of this one

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1. Any other DSM IV Axis I disorder
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3. Pregnancy - determined by history and if indicated, urine pregnancy test
4. Mothers who are breastfeeding (Added 21/06/2011)
5. Use of concomitant medication that would interfere in a pharmacodynamic or pharmacokinetic manner with metyrapone
6. Dependence on alcohol or other drug in the past 12 months and/or current harmful use of alcohol or other drug
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Date of first enrolment
01/02/2011

Date of final enrolment
30/11/2012

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Newcastle General Hospital
Newcastle Upon Tyne
United Kingdom
NE4 6BE

Sponsor information

Organisation
Northumberland, Tyne and Wear NHS Foundation Trust (UK)

ROR
https://ror.org/01ajv0n48

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Efficacy and Mechanism Evaluation Programme (ref: EME 08/43/39)

Alternative Name(s)
NIHR Efficacy and Mechanism Evaluation Programme, Efficacy and Mechanism Evaluation (EME), EME

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/06/2015		Yes	No
Results article	results	01/02/2016		Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes