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GENome-based therapeutic drugs for DEPression

Submission date	Recruitment status	[ ] Prospectively registered
13/08/2007	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
27/09/2007	Completed	[X] Results
Last Edited	**Condition category**	[ ] Individual participant data
04/10/2021	Mental and Behavioural Disorders	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2004-001723-38

Protocol serial number
EC Contract Ref.: LSHB-CT-2003-503428

Study information

Scientific Title
GENome-based therapeutic drugs for DEPression

Acronym
GENDEP

Study objectives
One in five people at some point in their lives suffer from an episode of depression severe enough to warrant antidepressant treatment. Although currently there is plenty of evidence for efficacy of antidepressants, a substantial minority of patients show an unsatisfactory response to medication, and cessation of taking prescriptions is common because of adverse side-effects. At present doctors do not have enough information to know how well patients will respond to one antidepressant over another. It is hoped that the genome-based therapeutic drugs for depression (GENDEP) project will lead to the development of a genetic test to assist doctors in choosing the right antidepressants for their patients and that it will advance understanding of the biological mechanisms responsible for an antidepressant being effective, which is important for the development of new and better treatments for depression.

This integrated project should lead to progress towards validated pharmacogenomic methods for symptom improvement, the prediction of response to psychiatric drug treatment and the reduction of adverse effects. It is hoped that it may also lead to greater basic understanding of the neurobiological mechanisms of depression, and hence be able to identify some promising leads for new targets for drug discovery.

We will initially genotype 10 to 13 candidate genes for which there are strong a priori hypotheses based upon existing genetic association data and/or the known pharmacodynamics and pharmacokinetics of the drugs. These candidate genes include those in the serotonin and noradrenaline pathways, specifically those implicated in the synthesis and re-uptake of the neurotransmitters plus selected receptors. Other important candidates are represented by cytochrome P450 enzymes implicated in drug metabolism, second messenger components, and neurotrophic factors. These will comprise the primary pharmacogenetic hypotheses of the study, and power calculations confirm that the sample is adequately powered to test these associations definitively. It is our aim in this study to identify the common genetic factors that determine response to antidepressants. By the end of the first phase of subject enrolment, other scientific elements of GENDEP will be generating candidate genes from the in vivo or in vitro studies, and other novel candidates may be generated by international research effort in this field. We will study a total of 10 to 13 candidates in the second wave of genotyping including those carried forward from the first wave (with the above replication analysis) on the N = 600, plus novel candidates on the N = 1000 available at the year 2.5 point. Protein and gene expression studies will also be conducted on a subset of the samples as outlined above.

Ethics approval required
Old ethics approval format

Ethics approval(s)
The Joint South London and Maudsley NHS Foundation Trust and Institute of Psychiatry Research Ethics Committee approved of this trial initially on the 16th April 2004 (full approval given on the 21st May 2004 [ref: 292/03]).

Study design

This is a randomised multi-centre partial cross-over trial designed to establish the genetic determinants of therapeutic response to two antidepressants with different mechanisms of action.

Primary study design
Interventional

Study type(s)
Screening

Health condition(s) or problem(s) studied
Major depressive episode

Interventions
Participants without contraindications to study medications will be randomised to receive either escitalopram or nortriptyline orally for 12 weeks. In case of non-response or adverse reaction, the treatment is terminated and, unless contraindicated, the other medication is offered for another 12 weeks. The crossover can occur at week 12 or earlier if clinically indicated with no washout period between the two treatments. Participants with a history of adverse effect, non-response or contraindication to one of the study medications are included and non-randomly allocated to the other medication. All participants will be followed up weekly for 12 weeks with an additional follow-up at week 26 from the start of the last course of medication.

1. Escitalopram initiated at 10 mg daily and titrated to a target dose of 20 mg daily within the first two weeks if tolerated; it can be further increased to a maximum dose of 30 mg daily if clinically indicated
2. Nortriptyline initiated at 50 mg daily and titrated to a target dose of 100 mg daily within the first two weeks if tolerated; further increase to a maximum dose of 200 mg daily is possible if clinically indicated

Participants without contraindications to study medications will be randomised to receive either escitalopram or nortriptyline for 12 weeks. In case of non-response or adverse reaction, the treatment is terminated and, unless contraindicated, the other medication is offered for another 12 weeks. Participants with a history of adverse effect, non-response or contraindication to one of the study medications are included and non-randomly allocated to the other medication.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Escitalopram, nortriptyline

Primary outcome(s)
1. 17-item Hamilton Depression Rating Scale (HDRS-17)
2. Montgomery-Asberg Depression Rating Scale (MADRS)
3. Beck Depression Inventory (BDI)

All primary hypotheses related to outcome and adverse reactions of medication will be based on the 8-week face-to-face assessment, controlling for the baseline values. These three measures will be integrated using Item Response Modelling.

Key secondary outcome(s))
1. Global Assessment Scale (GAS)
2. UKU side effects rating scale
3. Antidepressant side effect scale
4. Client Service Receipt Inventory (CSRI)
5. Temperament and Character Inventory - Revised (TCI-R)
6. Brief Life Events Questionnaire (BLEQ)
7. Sexual Functioning Questionnaire (SFQ)

Secondary analyses will include analysis of baseline data, and data up to week 12 and up to week 26. As there are many measures in this study and many time points, it is not possible to prestate all the secondary analyses that will be performed.

Completion date
31/12/2008

Eligibility

Key inclusion criteria
1. A diagnosis of major depressive episode of at least moderate severity, as defined by the International Classification of Diseases, version 10 (ICD-10) or the Diagnostic and Statistical Manual of mental disorders - fourth edition (DSM-IV) and established in the Schedules for Clinical Assessment in Neuropsychiatry interview (SCAN version 2.1, World Health Organisation [WHO], 1999)
2. White European parentage
3. Aged 18 to 65 years
4. Participants with mild depressive symptoms on antidepressant treatment can be included if there is a history of moderate or severe symptoms during the current depressive episode
5. Individuals aged over 65 can be included if they are medically fit and not taking regular medication other than antidepressants

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
1000

Key exclusion criteria
1. Family history of bipolar affective disorder or schizophrenia in first-degree relatives
2. A personal history of hypomanic or manic episode
3. Schizophrenia
4. Mood incongruent psychotic symptoms
5. Primary substance misuse
6. Primary organic brain disease
7. Current treatment with an antipsychotic or a mood stabiliser
8. Pregnancy or lactation
9. Medical contraindications or a history of lack of efficacy or adverse reaction to both study medications
10. Previous adverse reactions or non-response to either escitalopram or citalopram are considered as contraindications to escitalopram

Date of first enrolment
01/01/2004

Date of final enrolment
31/12/2008

Locations

Countries of recruitment
United Kingdom

England

Belgium

Croatia

Denmark

Germany

Italy

Poland

Slovenia

Study participating centre
Medical Research Council (MRC) Social, Genetic and Developmental Psychiatry (SGDP) Centre
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Sponsor information

Organisation
European Commission (Belgium)

ROR
https://ror.org/00k4n6c32

Funder(s)

Funder type
Government

Funder Name
European Commission (Belgium) (ref: LSHB-CT-2003-503428)

Alternative Name(s)
European Union, Comisión Europea, Europäische Kommission, EU-Kommissionen, Euroopa Komisjoni, EC, EU

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

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	15/10/2009		Yes	No
Results article	results	01/05/2010		Yes	No
Results article	results	01/07/2011		Yes	No

Results article	results	01/10/2011		Yes	No
Results article	results	01/11/2011		Yes	No
Results article	results	01/03/2012		Yes	No
Results article	results	01/02/2014		Yes	No
Results article	results	16/07/2019	19/07/2019	Yes	No
Results article	results	01/08/2019		Yes	No
Results article	results	03/01/2020	06/01/2020	Yes	No
Results article	Secondary analysis of inflammatory markers	28/09/2021	04/10/2021	Yes	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