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Bipolar Affective disorder: Lithium/ANti-Convulsant Evaluation

Submission date	Recruitment status
22/08/2005	No longer recruiting
Registration date	**Overall study status**
10/10/2005	Completed
Last Edited	**Condition category**
15/11/2013	Mental and Behavioural Disorders

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

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2004-001981-41

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
BALANCE 1

Study information

Scientific Title

Acronym
BALANCE

Study objectives
Combination therapy with lithium plus valproate semisodium is superior to either lithium or valproate monotherapy in the long term treatment of bipolar disorder.

For information:
1. Goodwin, G: Better data for bipolar disorder will help improve management. Keynote lecture. Progress In Neurology and Psychiatry -Guildford. 2004; 8(2): 26-30.
2. Rendell JM, Juszczak E, Hainsworth J, Van der Gucht E, Healey C, Morriss R, Ferrier N, Young AH, Young H, Goodwin GM, Geddes JR: Developing the BALANCE trial - the role of the pilot study and start-up phase. Bipolar Disorders 2004; 6(1): 26-31.
3. Rendell JM, Geddes JR, Ostacher MJ: Older patients are eligible for trial of lithium and valproate. BMJ 2003; 327: 395-96.
4. Geddes JR, Rendell JM, Goodwin GM: BALANCE: a large simple trial of maintenance treatment for bipolar disorder: World Psychiatry 2002; 1: 48-51.
5. Geddes JR: Can we conduct some large simple trials in bipolar disorder? Bipolar Disorders 2002; 4 (Suppl. 1): 62-63.
6. Geddes J, Goodwin G, Rendell J, Hainsworth J, Van Der Gucht E, Young H: New trial should clarify lithium use in bipolar disorder. BMJ 2002; 325:441.
7. Geddes J, Goodwin G: Bipolar disorder: clinical uncertainty, evidence-based medicine and large-scale randomised trials. Br.J Psychiatry 2001; 178:S191-S194.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Not specified

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Bipolar disorder

Interventions
1. Lithium monotherapy
2. Valproate semisodium monotherapy
3. Lithium plus valproate semisodium combination therapy

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Lithium, valproate semisodium

Primary outcome measure
1. Hospital admission: the primary outcome will be the time to hospital admission during the scheduled randomised treatment period. Admission is a useful indicator of a severe relapse of illness because, since bed provision is now minimal, the clinical threshold for admission is high. Admission to hospital is a useful pragmatic outcome: the majority of patients and clinicians view admission as a negative event that an effective maintenance treatment would be expected to prevent. In certain sites, because some mental health services use intensive alternatives to hospital treatment, the primary outcome will need to be a comparable administrative event such as new attendance at a day patient facility or active home treatment. The appropriate primary outcome will be established with each site before the trial starts and, for the purposes of the trial, a proxy must be 7 days per week treatment at day hospital or 7 days per week home treatment or 24 hour admission to flats and hostel accommodation under regular staff supervision.
2. Concurrent use of adjunctive medication: although there is general agreement that admission to hospital is a clinically meaningful and measurable outcome, it is a somewhat insensitive measure of the less severe mood fluctuations that cause considerable disability in bipolar disorder. Furthermore, manic episodes are more likely than depressive episodes to result in hospital admission. The use of adjunctive antidepressant and antipsychotic medication and of mood stabilizers other than lithium and valproate semisodium will provide a measure of the occurrence of mood episodes that are not severe enough to lead to admission.

Secondary outcome measures
1. Global Assessment of Functioning Scale (GAF): the GAF is a brief scale of overall functioning of demonstrated reliability and validity that is used in routine clinical practice and in recent trials in bipolar disorder. The GAF will be used to provide an overall estimate of functioning during the previous year.
2. Deliberate self-harm: deliberate self-harm of suicidal intent (including suicide) is a common outcome in bipolar disorder and of obvious clinical importance. There is observational evidence that lithium therapy reduces the incidence of suicide and it is important to measure this outcome, although it is unlikely that BALANCE will have sufficient power to detect a treatment effect reliably.
3. Quality of life: the EuroQol (EQ-5D) will be used to assess quality of life. This questionnaire

has been used successfully in two contemporary trials in psychiatry - the ongoing NHS R&D CUtLASS trial of atypical antipsychotics and the recent MRC-funded trial of cognitive behaviour therapy in bipolar disorder.
4. Adverse events: patients have identified adverse events and side-effects as being one of the main negative aspects of long term medication. Valproate semisodium is a newly licensed drug in the UK and it is essential to record the occurrence of all adverse events.
5. Withdrawal from study treatment: withdrawal from allocated treatment is a useful and pragmatic, although non-specific, measure of the overall acceptability and efficacy of a drug
6. Adherence to study medication: adherence to maintenance treatment is frequently overlooked in maintenance trials in bipolar disorder but is essential for interpreting the trial results

Overall study start date
01/07/2002

Completion date
31/12/2005

Eligibility

Key inclusion criteria
For entry to the run-in phase:
1. Previous episode of mania (clinical diagnosis, guided by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] criteria) that merited treatment (whether or not treatment was provided)
2. Agreement between investigator and patient to commence/continue treatment to prevent relapse
3. It is considered clinically reasonable to try combination treatment with lithium and valproate semisodium

For randomisation:
1. Uncertainty about which trial treatment would be best for the participant
2. Lithium plasma level 0.4 to 1.0 mmol/litre on stable dose of lithium
3. If valproate semisodium dose is less than 750 mg a day, the participant must have a valproic acid serum level of at least 50 µg/ml
4. The participant can tolerate the combination of lithium and valproate semisodium
5. Adherence during the run-in phase is judged satisfactory by the investigator

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
231

Key exclusion criteria

1. Maintenance treatment is considered unnecessary
2. A particular maintenance treatment is definitely indicated or contraindicated, or the patient is unwilling to take one or other of the study treatments
3. A medical disorder or condition coexists which contraindicates either of the investigational drugs, e.g., pregnancy
4. The patient is not normally resident in the UK or is of no fixed abode

Date of first enrolment
01/07/2002

Date of final enrolment
31/12/2005

Locations

Countries of recruitment
England

France

Germany

Ireland

Italy

United Kingdom

United States of America

Study participating centre
Department of Psychiatry
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Sponsor type
University/education

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ROR
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Funder(s)

Funder type
Industry

Funder Name
The Stanley Medical Research Institute (SMRI) (USA)

Funder Name
Sanofi-Aventis (UK)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	01/02/2002		Yes	No
Results article	results	30/01/2010		Yes	No