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Assessing the effectiveness of lithium plus quetiapine compared to lithium alone or quetiapine alone for treatment of adults with bipolar disorder

Submission date	Recruitment status	[ ] Prospectively registered
05/03/2025	Recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
19/06/2025	Ongoing	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
19/06/2025	Mental and Behavioural Disorders	[X] Record updated in last year

Plain English summary of protocol
Background and study aims
To evaluate the clinical and cost-effectiveness of combination lithium and quetiapine therapy compared with lithium or quetiapine alone for maintenance treatment in adults with bipolar disorder (BD).

The COMBINER trial is a pragmatic, phase 3, observer blind, multicentred, 3-arm, parallel group, randomisation-controlled trial with an internal pilot.
The trial is looking at two types of medication, lithium and quetiapine. These are used as maintenance treatment, which means patients are advised to take them in the longer term to reduce the risk of having major periods of depression or feeling elated. The trial is investigating whether these drugs taken together or on their own are better at reducing the chances that a person will experience these episodes in the longer term. We know both medications work, but we don't know which is better, or if combining the two could be best.

Who can participate?
We aim to recruit 303 people with bipolar who will be randomised between lithium, quetiapine, or both combined.

What does the study involve?
The COMBINER trial will run for 68 months altogether, with recruitment due to start in May 2025. Participants will be asked to take their randomised treatment for a follow up period of up to two years. Various assessments will let us answer the question of which treatment is best as a long term treatment to prevent mood episodes, but also the acceptability of each treatment to people with bipolar (e.g. symptoms, side effects) and things like quality of life and cost effectiveness. Participants will have 3 monthly remote follow up visits for 24 months, with more indepth and longer assessments at trial entry, year one, and year two.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
February 2025 to July 2029

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK).

Who is the main contact?
combiner@trials.bham.ac.uk

Contact information

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Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1010672

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
RG_24-081

Study information

Scientific Title
The effectiveness of lithium plus quetiapine COMBination versus lithIum versus quetiapiNe monothErapy in the maintenance treatment of bipolar disordeR: the COMBINER trial

Acronym
COMBINER

Study objectives
The primary objective is to evaluate whether a combination of lithium and quetiapine increases the time to next mood episode (e.g. mania or depression) over 24 months in comparison to monotherapy with lithium or quetiapine alone in the maintenance (i.e. long term) treatment of BD.

The secondary objective is to evaluate in the maintenance treatment of bipolar disorder:
1. The effectiveness of lithium vs quetiapine on time to next mood episode over 24 months.
2. The impact of lithium plus quetiapine vs lithium vs quetiapine on the following outcomes: time to next specified mood episode over 24 months, mania, depression, anxiety, health-related quality of life, functioning, side effects, patient acceptability, hospitalisation, service use, treatment adherence, occupational/educational outcomes, comorbid mental conditions, physical health, suicidal ideation, use of emergency medication, and time to stopping allocated

treatment.
3. The cost-effectiveness of lithium plus quetiapine vs lithium vs quetiapine.

Ethics approval required
Ethics approval required

Ethics approval(s)
Not yet submitted, to be confirmed, ref: 25/LO/0226

Study design
Interventional single blind randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

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

Interventions
Participants will be randomised in a 1:1:1 ratio to a combination of lithium and quetiapine or lithium or quetiapine.

Lithium (carbonate / citrate): initiation in line with usual practice or local Trust guidance, with plasma monitoring to reach a target plasma lithium level of 0.6-0.8 mMol/L, and titration to be individualised according to tolerability and participant characteristics, e.g. age.

Quetiapine: initiated at 50 mg/day. Titration to a target dose of 300-800 mg daily in line with usual practice or local Trust guidance, to be individualised according to tolerability and participant characteristics.

Trial medication will be prescribed and dispensed as in usual local practice with flexible, clinician/ patient driven choices on dosage adjustment and medication form (immediate or modified release). Titration will be over 4 weeks or more as required.

Participants will have 3 monthly remote follow up visits for 24 months, with more indepth and longer assessments at trial entry, year one, and year two.

Randomisation process:

Participants will be randomised at the level of the individual in a 1:1:1 ratio to lithium and quetiapine or lithium or quetiapine. Randomisation will be provided by BCTU using a secure online system, thereby ensuring allocation concealment.

Intervention Type
Drug

Pharmaceutical study type(s)
Dose response, Therapy

Phase
Phase III

Drug/device/biological/vaccine name(s)
Lithium carbonate, quetiapine fumarate

Primary outcome measure
Time to first new mood episode over 24 months post-randomisation measured using the Longitudinal Interval Follow-up Evaluation (LIFE) 3 monthly

Secondary outcome measures
1. Time to first new specified mood episode (mania, hypomania, mixed mood, depressive) over 24 months measured using the LIFE 3 monthly.
2. Number of weeks with mood episodes over 24 months measured using the LIFE 3 monthly.
3. Mania measured using the Young Mania Rating scare (YMRS) 3 monthly.
4. Depression measured using the Montgomery-Asberg Depression Rating Scale (MADRS) 3 monthly.
5. Anxiety measured using the General Anxiety Disorder-7 (GAD-7) at 6, 12, 18 and 24 months.
6. Patient acceptability measured using a visual analogue scale at 12 and 24 months.
7. Tolerability as measured using the UKU scale and Lithium Side Effect Rating Scale (LiSERS) at 12 and 24 months.
8. Time to stopping allocated treatment measured 3 monthly.
9. Treatment adherence measured using the Medication Adherence Rating Scale (MARS) 3 monthly and blood levels.
10. Suicidal ideation measured using the MADRS item 10 and Electronic Health Records (EHR) at 12 and 24 months.
11. Health-related quality of life as measured using the EQ-5D-5L at 6, 12, 18 and 24 months and the Quality of Life in Bipolar Disorder scale (QoL.BD) at 12 and 24 months.
12. Occupational and daily functioning measured using the Functioning Assessment Short Test (FAST) at 12 and 24 months.
13. Occupational/educational outcomes measured at 12 and 24 months.
14. Concomitant medication measured using Electronic Health Records (EHR) at 12 and 24 months.
15. Service utilisation measured using the Client Service Receipt Inventory (CSRI) at 6, 12, 18 and 24 months.
16. Hospitalisation, use of acute services, use of emergency medication, and comorbid mental health conditions measured using the EHR at 12 and 24 months.
17. Physical health (waist circumference, body mass index, blood pressure, random glucose and HbA1c) measured at 12 and 24 months.

Overall study start date
28/02/2025

Completion date
31/07/2029

Eligibility

Key inclusion criteria
1. Diagnosis of BD type I or II according to the DSM-5 confirmed by the Mini-International Neuropsychiatric Interview (MINI).
2. Aged ≥18 years.
3. Not currently in a mood episode (major depression, mixed episode, hypomania or mania) according to the DSM-5, defined as a score on the Longitudinal Interval Follow-up Evaluation (LIFE) of 4 or below.
4. If already on lithium or quetiapine, the patient and clinician are willing to consider the trial and potentially switch treatment.
5. Able to provide informed consent.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
303

Key exclusion criteria
1. Primary diagnosis of substance dependence or organic mood disorder.
2. Acute risk to self (clinician opinion).
3. Unstable medical illness that requires acute care (e.g. hospitalisation).
4. Contraindication to lithium or quetiapine:
4.1. Evidence of renal impairment (participant must have an eGFR ≥60 mls/min/1.73m² within two months prior to consent).
4.2. Medical conditions in which lithium use presents a risk (untreated hypothyroidism, Addison's disease, untreated epilepsy, cardiac insufficiency, rhythm disorders including Brugada syndrome or family history thereof, psoriasis)
4.3. Incompatible concurrent treatment (such as long term NSAID, diuretic, ACE-I or ARB) for a known medical condition for which no alternative treatment is available
5. Females of child-bearing potential only:
5.1. Pregnant. Note: Spot urine test will be performed before randomisation to rule out

pregnancy in females of child-bearing potential
5.2. Not willing to take highly effective contraceptive measures during the study intervention period AND for 30 days following the last trial medication dose.

Date of first enrolment
20/05/2025

Date of final enrolment
31/07/2027

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
-
United Kingdom
-

Sponsor information

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Sponsor type
University/education

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ROR
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Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care 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
Peer reviewed scientific journals
Internal report
Conference presentation
Publication on website
Other publication
Submission to regulatory authorities
Results will be sent to all participating centres who will notify the participants recruited from their site. Participants will be invited to discuss the study results with the local research team. Our PPI co-leads will be involved in determining and carrying out the best way of informing trial participants.

Intention to publish date
31/07/2030

Individual participant data (IPD) sharing plan
Requests for data generated during this study will be considered by BCTU (via bctudatashare@contacts.bham.ac.uk). Data will typically be available within six months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the Chief Investigator and, where appropriate (or in absence of the Chief Investigator) any of the following: the Trial Sponsor, the relevant Trial Management Group (TMG), and independent Trial Steering Committee (TSC).

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of patient identifiable information. Any data transfer will use a secure and encrypted method.

IPD sharing plan summary

Available on request