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A proof-of-concept study of an accessible lithium supplement

Submission date
25/07/2024

Recruitment status
Recruiting

Registration date
01/08/2024

Overall study status
Ongoing

Last Edited
04/07/2025

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol
Background and study aims:
Depression with mixed features (DMF) is where people experiencing a depressive episode also have symptoms of mania at the same time (for example, agitation, racing thoughts, reduced inhibition). DMF is common, occurring in up to a quarter of people with depression, and is associated with greater disability compared to depression without mixed features. DMF is particularly common in people with bipolar (spectrum) illnesses, and in people without a bipolar diagnosis is a significant risk factor for later receiving a bipolar diagnosis. The difficulties in treating DMF are well documented, and these challenges are compounded by the fact that DMF is often undetected in healthcare services and therefore not treated. (Full-dose) lithium is the gold standard medication for bipolar depression and mania, but is under-used because it requires frequent blood tests to ensure safety for patients. Our work, though, shows benefits of lower doses of lithium for depression and mania (when used alongside other medications) as well as cognitive function (e.g., memory). Because DMF includes symptoms of mania and depression (plus often cognitive difficulties), lower doses of lithium could be an effective add-on treatment. Mixed features are often not recognised in healthcare services, which reduces the potential for prescribed lithium. However, non-medication forms of lithium are available at a low dose (20mg) over-the-counter as a 'nutraceutical' ("LiOr") and could be accessible for many people to take, if found to be effective. My previous research shows that low-dose lithium is safe, and that – anecdotally – people find it helpful for low/fluctuating mood, cognition and agitation, all particularly relevant for DMF. However, LiOr's potential has not been explored in any reasonable-quality human studies.
This project will provide a 'proof of concept' to see whether LiOr could be assessed as a potential therapy at a large scale. We will recruit 40 people with DMF who are under stable ongoing treatment for depression, and measure 1) whether they agree to take 20mg LiOr daily, and how long they take it over a period of up to 6 months, 2) their levels of lithium in the blood, 3) any positive changes (e.g., to mood) over the 6-month study, 3) any negative effects or difficulties participants experience, 4) whether the measures and visits participants are asked to complete are acceptable for people. The results will give us enough information to plan a clinical trial, where LiOr can be robustly compared with a placebo to help determine whether LiOr could have benefits for people with DMF.

Who can participate?
We are looking for people aged 18 - 65 years, who are fluent in English, who do not have a diagnosis of bipolar disorder or are currently very suicidal but are having treatment for depression and have certain symptoms with their depression ('DMF'). People also have to be suitable and willing to try supplementary lithium and visit our research centre for measures 6 times over 6 months (as below).

What does the study involve?
Participants will be asked to visit our research centre 6 times over 6 months for a blood test and some questionnaires. Between visits they will be asked to take LiOr each day, so long as they are willing to do so during this time. After the first visit, we ask that the following visits are 2 weeks, 1 month, 2 months, 4 months and 6 months after the first visit.

What are the possible benefits and risks of participating?
We do not expect any significant risks or negative effects from taking part in the study. It is possible that people may feel some distress during blood tests or some of the questionnaires in visits. It is possible that people may not get on well with the lithium supplement, in which case they can lower the dose or stop taking it. On the other hand, we hope people will find benefits to mood and/or thinking skills and possibly other areas of life from the lithium supplement. Some people find the questionnaire visits interesting. Whether people experience benefits or not, findings from this study may help people in the future, as supplementary lithium is being tested to see if it is helpful for people experiencing a range of mood and brain conditions.

Where is the study run from?
South London and Maudsley NHS Foundation Trust (UK)

When is the study starting and how long is it expecting to run for?
July 2024 to January 2026

Who is funding the study?
Psychiatry Research Trust (UK)

Who is the main contact?
The study team's email address is lithium@kcl.ac.uk.
The lead researcher is Dr Rebecca Strawbridge, becci.strawbridge@kcl.ac.uk

Study website
https://www.kcl.ac.uk/research/mixli

Contact information

Type(s)
Public, Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
329291

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 329291

Study information

Scientific Title
Lithium orotate: a potential accessible supplement for people experiencing depression with mixed features.

Acronym
MixLi

Study objectives
To establish initial feasibility of studying a commercially available supplement (lithium orotate; LiOr) for its potential mood effects in people with depression including mixed features (DMF).

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 08/10/2024, Westminster Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 1048146; westminster.rec@hra.nhs.uk), ref: 24/LO/0620

Study design
Open label single arm proof of concept study

Primary study design
Interventional

Secondary study design

Non randomised study

Study setting(s)
Hospital, University/medical school/dental school

Study type(s)
Other

Participant information sheet
See outputs table

Health condition(s) or problem(s) studied
People experiencing an episode of depression with mixed features

Interventions
A lithium supplement which is currently available to purchase worldwide over the counter.
Formulation: Lithium orotate
Dose: up to 20 mg per day
Duration: Up to 6 months

Intervention Type
Supplement

Primary outcome measure
1. LiOr bioavailability is measured via lithium levels in serum (as per standard assay) at 2, 4, 8, 16 and 26 weeks from baseline.
2. LiOR acceptability is measured via self-report adherence (using the Tablet Routine Questionnaire) at baseline, 2, 4, 8, 16 and 26 weeks – and via discontinuation rates at the same time points.
3. LiOr subjective experiences is measured using participant-reported positive (using non-validated questions) and negative experiences (using the LiSERS scale) baseline, 2, 4, 8, 16 and 26 weeks.
4. Protocol feasibility - rates of recruitment, attrition and missing data (in putative primary outcome; below) at 2, 4, 8, 16 and 26 weeks from baseline.

Secondary outcome measures
1. Candidate biomarker changes i.e., c-reactive protein is measured (as per standard assay) at baseline, 2, 4, 8, 16 and 26 weeks.
2. Mood (putative primary outcome measure) changes are measured at baseline, 2, 4, 8, 16 and 26 weeks, using 1) the Maudsley visual analogue scales for depression and mania, 2) the internal states scale (ISS), 3) the generalised anxiety disorder 7-item questionnaire (GAD7), 4) the inventory of depressive symptoms (IDS) and 5) the young mania rating scale (YMRS).
3. Functioning and cognition (putative secondary measures) changes are measured at baseline, 2, 4, 8, 16 and 26 weeks, using 1) the Functional Assessment Short Test (FAST) and 2) the THINC-IT cognitive battery.

Overall study start date
25/07/2024

Completion date
31/01/2026

Eligibility

Key inclusion criteria
1. Aged between 18 - 65 years at study entry
2. Meet DSM-5 criteria for a current depressive episode (MINI) and exceed thresholds indicating presence of mixed features (Internal States Scale; ISS)
3. Undergoing stable pharmacological treatment for depression (intervention/dose unchanged for >6 weeks)
4. Willing to try a commercially available lithium supplement
5. Willing to attend planned study visits

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
Both

Target number of participants
40

Key exclusion criteria
1. Clinical diagnosis of bipolar disorder.
2. Other health condition that is severely impairing
3. Known contraindication to lithium treatment. This includes currently taking lithium
4. Unable to communicate fluently in English
5. Suicide risk

Date of first enrolment
28/10/2024

Date of final enrolment
30/11/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
South London and Maudsley NHS Foundation Trust
Bethlem Royal Hospital
Monks Orchard Road
Beckenham
United Kingdom
BR3 3BX

Sponsor information

Organisation
Institute of Psychiatry, Psychology & Neuroscience and South London & Maudsley NHS Foundation Trust joint office

Sponsor details
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Sponsor type
University/education

Website
https://www.kcl.ac.uk/ioppn/research/research-in-slam/rd-approval

Funder(s)

Funder type
Charity

Funder Name
Psychiatry Research Trust

Alternative Name(s)
The Psychiatry Research Trust, PRT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals as well as a variety of routes and forms accessible to the general public. We intend to publish the study protocol. A primary publication will include all primary and secondary outcomes as per the protocol.

Intention to publish date
31/07/2026

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Rebecca Strawbridge, becci.strawbridge@kcl.ac.uk, with the type of (anonymised) data depending on the request, available from 26 weeks after data collection has been completed, subject to participants' consent.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.1	18/09/2024	09/10/2024	No	Yes
Protocol file	version 1.2	08/10/2024	09/10/2024	No	No