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Clozapine in the treatment of borderline personality disorder. The CALMED study.

Submission date
18/03/2019

Recruitment status
No longer recruiting

Registration date
26/03/2019

Overall study status
Completed

Last Edited
09/08/2022

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
People with borderline personality disorder experience rapid and distressing changes in mood and difficulties in their relationships with others. These problems can lead to impulsive aggression, deliberate self-harm and suicide. People with borderline personality disorder are often given medication, but no drugs are licensed for this condition. In recent years doctors have tried using 'clozapine', an antipsychotic drug which is effective in treating other mental health conditions. There have been reports that it can improve mental health of inpatients with borderline personality disorder, but the drug has serious side effects which can be life-threatening and no clinical trials have been conducted.

Who can participate?
We will recruit people aged 18 years or over who are inpatients, have a confirmed diagnosis, and have failed to make an adequate response to existing treatment despite taking other antipsychotic drugs for at least three months. We will exclude people who have a clinical diagnosis of psychosis and those already taking clozapine.

What does the study involve?
We plan to conduct a randomised trial to examine the clinical and cost-effectiveness of clozapine versus placebo for inpatients with borderline personality disorder. We will recruit 222 people from inpatient services across England. At the start of the study we will assess patients' mental health, self-harm, aggressive behaviour, health-related quality of life, side effects of treatment and costs of care. Each person in the study would have an equal chance of receiving clozapine or placebo in addition to the care they would normally receive. Researchers will conduct follow-up assessments at three and six months, and will not know whether people are being prescribed clozapine or the placebo.

What are the possible benefits and risks of participating?
By taking part in this study, participants with will help us find out whether clozapine helps to improve the mental health of people who suffer from borderline personality disorder, and whether it reduces the time people spend in hospitals. As with any medicine, side effects are possible with clozapine, however, not everyone who takes the medication will experience problems. Another disadvantage is that patients will be asked to give blood on weekly basis for

18 weeks, and then every two weeks for the following 14 weeks. To reduce the risk of side effects, patients will receive a low dose of the study medication which is increases slowly. The most serious side effect of clozapine is agranulocytosis and for this reason, patients are required to have regular blood tests.

Where is the study run from?
Imperial College London

When is the study starting and how long is it expected to run for?
August 2019, 36 months

Who is funding the study?
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC)

Who is the main contact?
Dr Verity Leeson, v.leeson@imperial.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Verity Leeson

Contact details
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Additional identifiers

Clinical Trials Information System (CTIS)
2018-002471-18

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
39949

Study information

Scientific Title

The clinical effectiveness and cost effectiveness of clozapine for inpatients with borderline personality disorder: randomised controlled trial

Acronym
CALMED

Study objectives
The study primary hypothesis is that, for inpatients with borderline personality disorder, the addition of clozapine to usual treatment reduces symptoms of the disorder measured using the Zanarini Rating scale for Borderline Personality Disorder (ZAN- BPD).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/12/2018, Wales Research Ethics Committee 1 (Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB; 02920 785738; jagit.sidhu@wales.nhs.uk), ref: 18/WA/0382

Study design
Interventional randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Borderline personality disorder

Interventions
Study participants in the active arm of the trial will be prescribed a dose of up to 400mg of clozapine daily, depending on clinical response, patient preference and side effects.
Those in the control arm of the trial will be prescribed equivalent numbers of placebo capsules.
All those taking part in the study will continue to receive all other treatments as usual.
All study participants will be monitored in the same way regardless of the treatment arm they are in. There are three components to assessing and monitoring the health of people prescribed clozapine: full blood counts, monitoring of short term adverse events and long-term side effects of the drug physical health monitoring during initiation of treatment and continuing during trial treatment.

Remote web-based randomisation will be undertaken through a fully automated service operated by the NWORTH, University of Bangor. Randomisation will be via a secure online system using a sequentially randomised dynamic adaptive algorithm stratified by centre, ward type (general adult, low secure, medium secure and high secure) and gender (male or female). Within the algorithm, the likelihood of the participant being allocated to each treatment group is recalculated based on the participants already recruited and allocated. This recalculation is done at the overall allocation level, within stratification variables and within stratum level. By undertaking this re-calculation, the algorithm ensures that balance is maintained within acceptable limits of the assigned allocation ratio while maintaining unpredictability.

Intervention Type
Drug

Phase
Not Specified

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

Primary outcome(s)
Total score on the Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD) at six months (primary end point)

Key secondary outcome(s))
1. Total score on the Zanarini rating scale for Borderline Personality Disorder at three months.
2. General mental health using the Brief Psychiatric Rating Scale (BPRS) at three and six months.
3. Incidence and severity of suicidal behaviour using the Acts of Deliberate Self-Harm Inventory.
4. Level of aggressive behaviour using the Modified Overt Aggression Scale
5. Health related quality of life using the EQ-5D-5L.
6. Side effects of medication using the Antipsychotic Non-Neurological Side Effects Scale (ANNSERS) and motor and extrapyramidal side effects using the Extrapyramidal Side Effects Scale.
7. Incidence of withdrawal of trial medication due to adverse effects.
8. Medication adherence at three and six months using the Brief Adherence Rating Scale.
9. Resource use collected using a modified version of the Adult Service Use Schedule and by examining clinical records at six, 12 and 18 months. This will include detailed information about length of inpatient treatment and type of ward (high, medium, low secure, Psychiatric Intensive Care, general adult etc.), contacts with community mental health services and emergency medical services, and the type and dose of psychotropic medication that people are prescribed.

Completion date
31/07/2021

Eligibility

Key inclusion criteria
1. Aged 18 years or over
2. Currently an inpatient on a mental health unit
3. Meeting DSM-IV diagnostic criteria for borderline personality disorder
4. Failure to make an adequate clinical response to taking antipsychotic medication other than clozapine for at least three months
5. Satisfactory pre-treatment full blood count (white blood cell count > = 3.5 and absolute neutrophil count > = 2.0)
6. Weight and blood glucose recorded in their clinical records
(added 08/01/2020)
7. Have been an inpatient on a mental health ward for more than 28 days in the last 12 months, OR have had two or more admissions to hospital/ periods of care provided by Home Treatment over the last 12 months, AND a lifetime history of two or more incidents of harm to self or others which resulted in permanent damage/ disability, or would have done so had services not intervened

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
29

Key exclusion criteria
1. Current clinical diagnosis of schizophrenia, or bipolar I disorder
2. Prescribed clozapine within the last two weeks
3. Pregnant, trying to conceive, breastfeeding, or a woman of childbearing potential and is not using a highly
effective birth control.
4. Due to be discharged from the unit within the following two weeks and it is not possible to continue the necessary monitoring of physical health as an outpatient (updated 21/08/2019, previously: Due to be discharged from the unit within the following two weeks)
5. Unable to speak sufficient English to complete the baseline assessment
6. Unwilling or unable to provide written informed consent to take part in the study
7. Unable to undergo regular blood tests
8. Contraindication to clozapine or other listed condition, namely:
9. Known history of primary bone marrow disorders or impaired bone marrow function
10. Severe renal or cardiac disorders (e.g. myocarditis), or a known history of cardiac illness or abnormal cardiac findings on physical examination
11. Hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
12. Hypersensitivity to: Magnesium stearate; Silica, colloidal anhydrous; Povidone K30; Talc; Maize starch; Lactose monohydrate
13. History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy)
14. History of clozapine-induced agranulocytosis
15. Uncontrolled epilepsy
16. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions
17. Circulatory collapse and/or CNS depression of any cause
18. Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure
19. Paralytic ileus

Date of first enrolment
01/09/2019

Date of final enrolment
04/03/2021

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Central and North West London NHS Foundation Trust
1st Floor Bloomsbury Building
St Pancras Hospital
4 St Pancras Way
London
United Kingdom
NW1 0PE

Study participating centre
West London Mental Health NHS Trust
1st Floor, Wing B
1 Armstrong Way
Southall
London
United Kingdom
UB2 4SD

Study participating centre
Merseycare NHS Foundation Trust
Trust Headquarters
Kings Business Park
Prescot
United Kingdom
L34 1PJ

Study participating centre
Lancashire Care NHS Foundation Trust
Vicarage Lane
Fulwood
Preston
United Kingdom
PR2 8DW

Study participating centre
Nottinghamshire Healthcare NHS Foundation Trust
Duncan MacMillan House
Porchester Road
Mapperley
Nottingham
United Kingdom
NG3 6AA

Study participating centre
Elysium Healthcare
Chadwick Drive
off Saxon Street
Eaglestone
Milton Keynes
United Kingdom
MK6 5LT

Study participating centre
St Andrew's Healthcare
Cliftonville
Northampton
United Kingdom
NN1 5DG

Sponsor information

Organisation
Imperial College of Science, Technology and Medicine

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
National Institute for Health 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

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Mike Crawford (m.crawford@imperial.ac.uk).
1. Type of data that will be shared: de-identified participant-level data including primary and secondary outcome measures, and adverse events.
2. When the data will become available and for how long: from 01/01/2022 with no fixed end date
3. By what access criteria data will be shared including with whom, for what types of analyses, and by what mechanism: data may be accessed by researchers who provide a methodologically sound proposal by email to Prof. Crawford
4. Whether consent from participants was obtained: all participants gave written informed consent
5. Comments on data anonymisation: any data that could potentially be used to identify participants will not be provided in the dataset at the individual participant level e.g. ethnicity, dates of service use

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		29/04/2022	09/08/2022	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	version v3	01/05/2019	29/10/2019	No	Yes
Participant information sheet	version v4	26/12/2019	08/01/2020	No	Yes
Participant information sheet	version v5.0	11/02/2020	15/07/2020	No	Yes
Protocol file	version v9 version v2	08/12/2020	04/03/2021	No	No

Statistical Analysis Plan	08/07/2021	22/07/2021	No	No