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Investigating the use of clozapine in young people with psychosis

Submission date
10/08/2022

Recruitment status
No longer recruiting

Registration date
16/11/2022

Overall study status
Completed

Last Edited
16/07/2025

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
Schizophrenia is a condition that causes symptoms like delusions, hallucinations, reduced motivation and muddled thinking. Schizophrenia usually starts in the twenties but can begin earlier, when it is often more severe. The main treatment is antipsychotic medication; if untreated, symptoms typically continue for many years. One antipsychotic, clozapine, works better than any other and has the best chance of working if started early on in treatment. On the other hand, clozapine has more side effects than some other antipsychotics, so doctors only use it when other drugs haven't helped. For this reason, almost all research on clozapine was done with adults who had already taken other antipsychotics. Research in children and young people with schizophrenia shows that antipsychotics do help them, but there is little research focussed on clozapine. Three studies suggest that clozapine works better than other antipsychotics in children and young people, but the studies were too small to be conclusive and doctors still don’t use it often, leading to enduring symptoms. Therefore we will study clozapine as a treatment for schizophrenia in young people, recruiting only people <25 years old and trying to recruit as many as possible aged <18 years.

Who can participate?
People under 25 years old and trying to recruit as many as possible aged under 18 years. We will include 50 people, recruited across various hospital clinics and services within the UK, who are still symptomatic after treatment with at least two antipsychotics.

What does the study involve?
A computer will decide randomly whether each person will take clozapine or any other antipsychotic for 12 weeks. Researchers will assess their symptoms several times without knowing which drug they are taking to avoid biases. At the end of the study, towards the end of 2026, we will see if clozapine reduced people’s symptoms more than other antipsychotics, their side effects, how well they feel, how much their treatment costs and how often they need hospital treatment. After the study is over, we will contact them again to see how they are doing in the longer term.

Some participants in the clinical trial will additionally be asked to complete a magnetic resonance imaging (MRI) brain scan and provide a blood sample, once at the beginning and once

at the end of the twelve-week period. The MRI scans will be used to measure glutamate and related aspects of brain structure and function. The blood samples will be used to measure proteins in the blood involved in inflammation, such as cytokines. At the end of the study, we will see if the biological measures in the brain and blood change more during treatment with clozapine compared to other antipsychotics, and how they relate to the amount that symptoms improve.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
People with schizophrenia are routinely treated with antipsychotic medication as part of their usual care, and the participants will also be treated with antipsychotic - it is only the choice of antipsychotic that will be determined by the trial. The potential risks and burdens for research participants will thus be the same as standard care. To minimise side effects, clinicians will have complete freedom to adjust the dose to achieve the best balance between therapeutic and adverse effects. Treatment to combat side effects can also be given to participants in the same way as with usual care. Advice to prevent common side effects such as weight gain and sedation will be given at the beginning of the trial. Participants might not respond to treatment. Nonetheless, after the first 12 weeks of trial, treatment can be changed while remaining in the study for longer-term outcome.

Where is the study run from?
King’s College London (UK)

When is the study starting and how long is it expected to run for?
August 2022 to October 2026

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

Who is the main contact?
1. Dr James MacCabe, james.maccabe@kcl.ac.uk
2. Laura Marchant, Laura.marchant@kcl.ac.uk
3. Prof. Alice Egerton (embedded mechanistic study), Alice.Egerton@kcl.ac.uk

Contact information

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-006248-28

Integrated Research Application System (IRAS)
1004947

Central Portfolio Management System (CPMS)
53859

Study information

Scientific Title
CLEAR: (CLozapine in EARly psychosis) A Multi-Centre, Observational Study of Clozapine for Young People with Treatment-Resistant Psychosis in Real World Settings

Acronym
CLEAR

Study objectives
The primary objective is to compare the treatments on the change in total PANSS score from baseline to 12 weeks.
The secondary objectives are to compare the treatments on function, side effects, quality of life, subjective improvement and cost-effectiveness.

Added 01/02/2023:
In addition, in an embedded mechanistic study we will test the hypothesis that, compared to other antipsychotics, treatment with clozapine is associated with a greater reduction in proinflammatory cytokines, brain glutamate and regional cerebral blood flow, and an increase in anti-inflammatory cytokines and glutathione.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/12/2022, London - Dulwich Research Ethics Committee (Health Research Authority, Skipton House, 80 London Road, London, SE1 6LH, UK; +44 (0)2071048089; dulwich.rec@hra.nhs.uk), ref: 22/LO/0605

Primary study design
Observational

Study design
Observational non-randomized study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Treatment-resistant psychosis

Interventions
Current interventions as of 16/07/2025:
Multi-centre, open-label, blind-rated (primary outcome), 1:1 observational study of clozapine versus treatment as usual in children and young people (<25) with treatment-resistant schizophrenia.

Intervention: Clozapine, oral, flexible dose within dose range defined by British National Formulary (BNF); (Maximum dose = 900 mg per day), at the discretion of the prescriber, for 12 weeks. Following this, if clozapine is continued, it will no longer be classified as an investigational medicinal product.

Control: Any oral antipsychotic in the TAU group ATC code – N05A (other than clozapine ATC code – N05AH02 and Lithium – N05AN), within licensed dose range defined by BNF, for 12 weeks. The choice of antipsychotic will be agreed by the clinical team in collaboration with the participant, and the dose titrated to achieve the best balance between response and adverse effects.

Participants in both arms will be followed up at week 2, week 6 and week 12. Following this it will be a clinical decision as to whether the participant continues on the same medication, or switches to a different one.

This trial is a single-blind, observational trial. The raters will be centralised and blinded to minimise observer bias. Initially a randomisation system was created in collaboration with the trial analyst/s and the CI and hosted on a dedicated server. However, from Protocol v8.0 participants are no longer randomized and patients make their own treatment decision.

The blood samples will be collected in a subset of participants and used to measure levels of pro- and anti-inflammatory cytokines and GSH.

Previous interventions:
Multi-centre, open-label, blind-rated (primary outcome), 1:1 randomised controlled effectiveness trial of clozapine versus treatment as usual in children and young people (<25) with treatment-resistant schizophrenia.
Intervention: Clozapine, oral, flexible dose within dose range defined by British National Formulary (BNF); (Maximum dose = 900 mg per day), at the discretion of the prescriber, for 12 weeks. Following this, if clozapine is continued, it will no longer be classified as an investigational medicinal product.
Control: Any oral antipsychotic in the TAU group ATC code – N05A (other than clozapine ATC code – N05AH02 and Lithium – N05AN), within licensed dose range defined by BNF, for 12 weeks. The choice of antipsychotic will be agreed upon by the clinical team in collaboration with the participant, and the dose titrated to achieve the best balance between response and adverse effects.

Participants in both arms will be followed up at week 2, week 6 and week 12. Following this it will be a clinical decision as to whether the participant continues on the same medication, or switches to a different one and they will be followed up for 12 months through clinical notes and, whenever possible, videolink assessments (week 24 and 52).
This trial is a single-blind, randomised, controlled trial. The raters will be centralised and blinded to minimise observer bias. A web-based randomisation system will be designed, using the bespoke KCTU randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL.

Added 01/02/2023:
Additionally, in an embedded mechanistic study, brain Magnetic Resonance Imaging (MRI) scans and blood samples will be acquired at baseline and 12 weeks in a subset of participants. The MRI session will include acquisition of structural images, proton magnetic resonance spectroscopy (1H-MRS) to measure levels of glutamate, GSH and other brain metabolites and arterial spin labelling to measure regional cerebral blood flow. The blood samples will be used to measure levels of pro- and anti-inflammatory cytokines and GSH.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)

Clozapine

Primary outcome(s)
Change in total PANSS score from baseline to 12 weeks.

Key secondary outcome(s)
Current secondary outcome measures:
Assessment will take place at weeks 6 and 12:
1. Change in overall clinical impression (CGI)
2. Clinician rated level of adherence (CRS)
3. Side effects (GASS-C)
4. Quality of life (EQ-5D-Y)
5. Subjective experience (DAI-10)
6. Psychotropic treatment, service use and readmission rate, (EI-AD-SUS)
7. Change in PANSS sub-scale (positive, negative and general), and weight gain

Previous secondary outcome measures:
Assessment will take place at weeks 6, 12, 24 and 52:
1. Change in overall clinical impression (CGI)
2. Clinician rated level of adherence (CRS)
3. Side effects (GASS-C)
4. Quality of life (EQ-5D-Y)
5. Subjective experience (DAI-10)
6. Psychotropic treatment, service use and readmission rate, (EI-AD-SUS)
7. Change in PANSS sub-scale (positive, negative and general), and weight gain

Added 01/02/2023:
In the embedded mechanistic study, outcomes will include, from baseline to 12 weeks:
1. Change in brain glutamate, measured using proton magnetic resonance spectroscopy (1H-MRS)
2. Change in brain glutathione, measured using 1H-MRS
3. Change in regional cerebral blood flow, measured using arterial spin labelling
4. Change in peripheral levels of glutathione and cytokines

Completion date
31/10/2026

Eligibility

Key inclusion criteria
Current inclusion criteria as of 16/07/2025:
1. Age ≥12 and <25 years at baseline
2. Meets criteria for schizophrenia or related disorder, in the range ICD-10v2016 F20.x, F22.x-F29.x
3. Meets NICE criteria for treatment resistance, defined as:
3.1. Previous trials of at least two different antipsychotic drugs with adequate adherence (estimated <20% missed doses) – both treatment trials to exceed 4 weeks at adequate doses (within the dose range given in the British National Formulary and the British National Formulary for children)
3.2. At least 1 of these trials must be with a second-generation drug
4. Positive and Negative Syndrome Scale (PANSS) total ≥70, at least 2 items >4

5. Clinician Rating Scale [24] (CRS) ≥3
6. Capacity to give informed consent OR has a legal representative able to give consent to the trial

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Previous inclusion criteria as of 24/04/2025:

1. Age ≥12 and <25 years at randomisation
2. Meets criteria for schizophrenia or related disorder, in the range ICD-10v2016 F20.x, F22.x-F29.x
3. Meets NICE criteria for treatment resistance, defined as:
3.1. Previous trials of at least two different antipsychotic drugs with adequate adherence (estimated <20% missed doses) – both treatment trials to exceed 4 weeks at adequate doses (within the dose range given in the British National Formulary and the British National Formulary for children)
3.2. At least 1 of these trials must be with a second-generation drug
4. Positive and Negative Syndrome Scale (PANSS) total ≥70, at least 2 items >4
5. Clinician Rating Scale [24] (CRS) >3
6. English or Welsh language sufficient to participate
7. Capacity to give informed consent OR has a legal representative able to give consent to the trial

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Previous inclusion criteria as of 13/03/2024:

1. Age ≥12 and <25 years at randomisation
2. Meets criteria for schizophrenia or related disorder, in the range ICD-10v2016 F20.x, F22.x-F29.x
3. Meets NICE criteria for treatment resistance, defined as:
3.1. Previous trials of at least two different antipsychotic drugs with adequate adherence (estimated <20% missed doses) – both treatment trials to exceed 6 weeks at therapeutic dose (≥600 mg chlorpromazine equivalent).
3.2. At least 1 of these trials must be with a second-generation drug.
3.3. Failure to respond to NICE-recommended psychological treatment OR failure to engage in same.
4. Positive and Negative Syndrome Scale (PANSS) total ≥70, at least 2 items >4
5. Clinician Rating Scale [24] (CRS) >3.
6. English or Welsh language sufficient to participate.
7. Capacity to give informed consent OR has a legal representative able to give consent to the trial.

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Previous inclusion criteria:

1. Age ≥12 and <25 years at randomisation
2. Meets criteria for schizophrenia or related disorder, in the range ICD-10v2016 F20.x, F22.x-F29.x
3. Meets NICE criteria for treatment resistance, defined as:
3.1. Previous trials of at least two different antipsychotic drugs with adequate adherence

(estimated <20% missed doses) – both treatment trials to exceed 6 weeks at therapeutic dose (≥600 mg chlorpromazine equivalent).
3.2. At least 1 of these trials must be with a second-generation drug
3.3. Failure to respond to NICE-recommended psychological treatment OR failure to engage in same
4. Positive and Negative Syndrome Scale (PANSS) total ≥70, at least 2 items >4
5. Compliance Rating Scale [23] (CRS) >3
6. English or Welsh language sufficient to participate
7. Capacity to give informed consent OR has a consultee (normally a family member) able to give consent to the trial.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
12 Years

Upper age limit
24 Years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 16/07/2025:
1. Psychosis predominantly caused by substance misuse.
2. Pregnancy.
3. Breastfeeding.
4 Women of child-bearing potential (WOCBP*) not using at least acceptable methods of contraception** during the trial
5. Previous adequate trial of clozapine.
6. CNS disorders (ICD-10 G00-26; G40-41, G45-46; G80-94, G97).
7. Concurrent medications with documented interactions with antipsychotics.
8. Participation in a clinical trial involving any unlicensed investigational medical product (within the last 3 months.
9. Positive test for COVID-19 within the past 10 days.
10. Current Electroconvulsive Therapy (ECT)

* WOCBP defined as: fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
** acceptable methods of contraception include:
• progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

• male or female condom with or without spermicide ***
• cap, diaphragm or sponge with spermicide ***
*** A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods
Acceptable methods are the minimum requirement. It should be noted that the requirement for 'at least acceptable methods of contraception' would include the above methods but also include all 'highly effective' methods listed below:
1. Combined (estrogen and progestogen containing) hormonal
2. Contraception associated with inhibition of ovulation 1:
2.1. Oral
2.2. Intravaginal
2.3. Transdermal
3. Progestogen-only hormonal contraception associated with inhibition of ovulation 1:
3.1. Oral
3.2. Injectable
3.3. Implantable
4. Intrauterine device (IUD)
5. Intrauterine hormone-releasing system (IUS)
6. Bilateral tubal occlusion
7. Vasectomised partner
8. Sexual abstinence (if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)

Previous exclusion criteria as of 13/03/2024:
1. Psychosis predominantly caused by substance misuse.
2. Pregnancy.
3. Breastfeeding.
4 Women of child-bearing potential (WOCBP*) not using at least acceptable methods of contraception** during the trial
5. Contraindications to clozapine as listed in SmPC as follows:
5.1. Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1.
5.2. Patients unable to undergo regular blood tests.
5.3. History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
5.4. History of clozapine-induced agranulocytosis.
5.5. Impaired bone marrow function.
5.6. Uncontrolled epilepsy.
5.7. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
5.8. Circulatory collapse and/or CNS depression of any cause.
5.9. Severe renal or cardiac disorders (e.g. myocarditis).
5.10. Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
5.11. Paralytic ileus.
5.12. Clozapine treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged.
6. Previous adequate trial of clozapine.
7. CNS disorders (ICD-10 G00-26; G40-41, G45-46; G80-94, G97).
8. Concurrent medications with documented interactions with antipsychotics.
9. Participation in a clinical trial involving any investigational medical product (licensed or unlicensed) within the last 3 months.

10. Positive test for COVID-19 within the past 10 days.
11. For participation in the substudy MRI scan only, standard contraindications to MRI at 3 Tesla such as ferromagnetic or electronic implants.

* WOCBP defined as: fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
** acceptable methods of contraception include:
• progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
• male or female condom with or without spermicide ***
• cap, diaphragm or sponge with spermicide ***
*** A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods
Acceptable methods are the minimum requirement. It should be noted that the requirement for 'at least acceptable methods of contraception' would include the above methods but also include all 'highly effective' methods listed below:
1. Combined (estrogen and progestogen containing) hormonal
2. Contraception associated with inhibition of ovulation 1:
2.1. Oral
2.2. Intravaginal
2.3. Transdermal
3. Progestogen-only hormonal contraception associated with inhibition of ovulation 1:
3.1. Oral
3.2. Injectable
3.3. Implantable
4. Intrauterine device (IUD)
5. Intrauterine hormone-releasing system (IUS)
6. Bilateral tubal occlusion
7. Vasectomised partner
8. Sexual abstinence (if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments).

Previous exclusion criteria:
1. Psychosis predominantly caused by substance misuse
2. Pregnancy
3. Breastfeeding
4. Contra-indications to clozapine as listed in BNF SmPC as follows:
4.1. Hypersensitivity to the active substance or to any of the excipients
4.2. Patients unable to undergo regular blood tests.
4.3. History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
4.4. History of clozapine-induced agranulocytosis.
4.5. Impaired bone marrow function.
4.6. Uncontrolled epilepsy.
4.7. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
4.8. Circulatory collapse and/or CNS depression of any cause.
4.9. Severe renal or cardiac disorders (e.g. myocarditis).
4.10. Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.

4.11. Paralytic ileus.
4.12. Clozapine treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged.
5. Previous adequate trial of clozapine
6. CNS disorders (ICD-10 G00-26; G40-41, G45-46; G80-94, G97).
7. Concurrent medications with documented interactions with antipsychotics
8. Participation in a medicinal trial involving an unlicensed, investigational medical product within the last 3 months
9. Positive test for COVID-19 within the past 10 days.

Date of first enrolment
24/11/2023

Date of final enrolment
31/08/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Bethlem Royal Hospital
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Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Organisation
South London and Maudsley NHS Foundation Trust

ROR
https://ror.org/015803449

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

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		14/02/2024	15/02/2024	Yes	No
Protocol file	version 4.0	01/08/2023	13/03/2024	No	No
Protocol file	version 6.0	27/08/2024	24/04/2025	No	No
Protocol file	version 8.0	19/05/2025	16/07/2025	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes