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A trial of medications in comparison to dummy tablets for the treatment of drooling caused by clozapine.

Submission date
05/12/2023

Recruitment status
Recruiting

Registration date
26/01/2024

Overall study status
Ongoing

Last Edited
23/08/2024

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
Clozapine is an antipsychotic medication used to help treat the symptoms of schizophrenia and is also sometimes used to treat other mental health conditions. It is the most effective antipsychotic medication for many people and it is important to keep taking it. Clozapine can cause different side effects and people tell us one of the most upsetting is excessive drooling. Doctors call this 'clozapine-induced hypersalivation' (CIH or drooling). People with CIH/drooling tell us they often have to wipe the saliva from their mouth during the day and their pillow becomes very wet at night which can sometimes make the skin on their face sore. CIH can be very embarrassing and lead to some patients wanting to stop clozapine treatment. For most patients this is not a good idea as their mental illness is likely to come back and they may need to be admitted to hospital. Currently, there is no proven treatment for CIH. The medication usually prescribed is called hyoscine but we don't know if hyoscine helps although doctors think it might. Hyoscine can cause unpleasant side effects such as bowel problems (constipation) and thinking problems (making attention and concentration worse). Some studies suggest a different medication called glycopyrrolate might be helpful for CIH and may cause fewer thinking problems. But it may still cause other side effects like constipation. Patients have told us that it is important for them to know which medications may improve CIH and what the side effects are so they can make an informed choice about whether or not to take any of these medicines based on their mental illness symptoms and experience of side effects. Our study will find out if either hyoscine or glycopyrrolate can improve CIH/drooling by comparing patients taking these medications with patients taking a dummy treatment (placebo). If both help reduce CIH/drooling we will compare the two medications to see which one causes fewer side effects and ask which one patients prefer.

Who can participate?
Patients aged 18 - 65 years, with clozapine-induced hypersalivation.

What does the study involve?
Participants will be randomly assigned to receive either hyoscine hydrobromide, glycopyrronium bromide (glycopyrrolate), or a placebo over a period of 12 weeks.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
Burden of visits and assessments: Treatment visits have been aligned with routine care clozapine clinic visits (every 4 weeks). Visits at home instead of the clozapine clinic can be arranged if participants prefer. Service users have been involved in GOTHIC2 throughout its development. The participant pathway and all patient-facing documentation have been developed with full PPIE involvement and use of the FAST-R service.
Treatment Intervention: A summary of the more important risks are as follows:
Hyoscine hydrobromide (Kwells): Very common side effects (more than one in 10) include feeling a bit sleepy or dizzy, eyesight being a bit blurry and having a dry mouth. Constipation is also possible. All of these side effects can also happen with clozapine (nIMP) so participants may not notice any difference. There is a very small chance participants might find it more difficult to concentrate or think clearly. The comprehensive list of undesirable effects is listed in the relevant SmPC.
Side effects from a placebo are unlikely as it is a dummy capsule with inactive ingredients. The main ingredient, Magnesium stearate, is generally safe to consume but too much of it can have a laxative effect.
Glycopyrronium bromide (Glycopyrrolate): Very common side effects (more than 1 in 10) include dry mouth, constipation, diarrhoea, vomiting, flushed skin, nasal congestion, having difficulty emptying the bladder (urinary retention), feeling irritable and experiencing a reduction in chest secretions. Common side effects (experienced by one in 10 to 1 in 100 people) include chest infections (including pneumonia), urine infections, feeling agitated or drowsy, nose bleeds, rash and fever. The comprehensive list of undesirable effects is listed in the relevant SmPC.
Placebo side effects are unlikely as it is a dummy capsule with inactive ingredients. The main ingredient, Magnesium stearate, is generally safe to consume but too much of it can have a laxative effect. This is also a component of clozapine (nIMP).
Treatment modifications: trial participants should not be prescribed any other CIH treatment. Participants are prescribed two capsules per day in week one and three capsules per day from week two until the end of treatment at week twelve. Should the treating clinician have any concerns about tolerance then the dose may be reduced in week one to one capsule per day and the dose can be reduced in weeks 2-12 to one or two capsules per day. The reduction and reason for the reduction should be recorded in the appropriate eCRF.
Dose modifications: Participants who discontinue clozapine treatment should also discontinue trial treatment. The discontinuation of trial treatment and reason must be recorded in the appropriate eCRF.

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

When is the study starting and how long is it expected to run for?
November 2023 to May 2027

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

Who is the main contact?
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Contact information

Type(s)
Public, Scientific

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Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1008055

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
UoL001694, IRAS 1008055, CPMS 58120

Study information

Scientific Title
A 3-arm multi-centre randomised placebo-controlled trial of glycopyrrolate or hyoscine hydrobromide for the treatment of clozapine-induced hypersalivation

Acronym
GOTHIC2

Study objectives
Primary objective:
To ascertain the efficacy of either hyoscine hydrobromide or glycopyrrolate in comparison to placebo in the treatment of CIH.

Secondary objectives:
1. To establish which of glycopyrrolate or hyoscine hydrobromide, if any, is associated with fewer cognitive side-effects using a validated assessment measure.
2. To establish which of glycopyrrolate or hyoscine hydrobromide, if any, is associated with fewer ADRs.

Open-label objectives:
1. To increase knowledge of the safety profile of the active IMPs in the treatment of CIH.
2. To establish the effectiveness of active IMPs over the open-label phase.

Updated 01/05/2024:
Exploratory objective:
1. To establish whether clozapine plasma levels are associated with clozapine ADRs (moved from secondary objectives)

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 24/01/2024, London - Fulham Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8084, (0)207 104 8286; fulham.rec@hra.nhs.uk), ref: 23/LO/1002

Study design
Interventional double-blind randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet
Anyone interested can contact the LCTC trial team at gothic2@liverpool.ac.uk for most up to date version of trial documentation.

Health condition(s) or problem(s) studied

Clozapine induced hypersalivation (CIH)

Interventions
Participants will be randomised via a secure (24-hour) web-based randomisation system controlled centrally by the LCTC to receive either hyoscine hydrobromide, glycopyrronium bromide (glycopyrrolate) or placebo in a ratio of 1:1:1

Route of administration: capsules for oral administration

IMP1: Hyoscine hydrobromide (over-encapsulated)
Dose: Week 1: 300 micrograms (1 capsule) twice daily
Week 2-12: 300 micrograms (1 capsule) three times daily

IMP2: Glycopyrronium bromide (Glycopyrrolate) (over-encapsulated)
Dose: Week 1: 1 mg (1 capsule) twice daily
Week 2-12: 1 mg (1 capsule) three times daily

Placebo: capsules filled with Lactose & Magnesium Stearate blend
Dose: Week 1: 1 capsule twice daily
Week 2-12: 1 capsule three times daily

Trial treatment duration is 12 weeks with an optional 12 week open-label follow up period.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacokinetic, Pharmacodynamic, Therapy

Phase
Phase III

Drug/device/biological/vaccine name(s)
Hyoscine Hydrobromide [Hyoscine Hydrobromide 300 microgram] , Glycopyrronium Bromide [Glycopyrronium Bromide]

Primary outcome measure
Hypersalivation measured using the Drooling Rating Scale at Baseline, T 1, 2, 4, 6, 8, 12 and Optional T16, 20, 24

Secondary outcome measures
1. Neuroleptic side-effects measured using the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) PROM (participant reported outcome measure) at Baseline, T 4, 8, 12 and Optional T16, 20, 24
2. Anticholinergic side effects measured using the Liverpool Anticholinergic Side-effects Scale (LASS) PROM at Baseline, T 4, 8, 12 and Optional T16, 20, 24
3. Sustained attention and Verbal Recognition Memory (VRM) measured using the Cambridge Neuropsychological
Test Automated Battery (CANTAB) via a pre-loaded tablet device at Baseline and T12
4. Nocturnal hypersalivation measured using the Nocturnal Hypersalivation Rating Scale (NHRS) PROM at Baseline, T 1, 2, 4, 6, 8, 12 and Optional T16, 20, 24

5. Self-esteem measured using the Rosenberg Self-esteem scale (RSE) PROM at Baseline and T12
6. Hospital admission (whether for physical or psychiatric reasons) from Consent up to T12 and Optional follow-up to T24
7. Constipation measured using the Patient assessment of constipation and symptoms (PAC-SYM) at Baseline, T4, 8, 12 and Optional T24
8. Social functioning measured using the Personal and Social Performance scale (PSP) conducted via interview at Baseline and T12
9. Symptoms of schizophrenia measured using the Positive and negative syndrome scale (PANSS) conducted via interview at Baseline and T12
10. Effect and tolerability of treatment measured by premature discontinuation of study treatment/Continuation at T12
11. Discontinuation of clozapine
12. Serious Adverse Events reported from Consent up to T12 and Optional follow-up to T24

Updated 01/05/2024:
Exploratory outcome measure:
1. Clozapine plasma levels from blood analysis at Baseline and T12 (moved from secondary outcome measures)

Overall study start date
30/11/2023

Completion date
20/05/2027

Eligibility

Key inclusion criteria
1. Aged 18 to 65 years inclusive.
2. English speaking.
3. Prescribed clozapine for a minimum of three months.
4. Experiencing hypersalivation with a minimum score of 4 on the Drooling Rating Scale (DRS) and are either:
4.1. Currently not receiving treatment for CIH, OR
4.2. Receiving drug treatment for CIH and agreeable to a 48-hour washout period
5. Written and informed consent obtained from participant (with capacity and ability) and agreement of participant to comply with the requirements of the trial prior to study specific procedures.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
Both

Target number of participants
252

Key exclusion criteria
Current participant exclusion criteria as of 07/03/2024:
1. Medical conditions that could influence hypersalivation (e.g., Parkinson's Disease).
2. Neurological conditions that could affect cognitive functioning during the course of the study (e.g., unstable epilepsy).
3. History of an allergic reaction to hyoscine hydrobromide
4. History of an allergic reaction to glycopyrrolate.
5. Any of the following contra-indications to hyoscine hydrobromide or glycopyrrolate as stated in the British National Formulary:
5.1. Prostatic enlargement
5.2. Myasthenia gravis
5.3. Pyloric stenosis
5.4. Paralytic ileus
5.5. Glaucoma
5.6. Hepatic Impairment
6. Any of the following cautions to hyoscine hydrobromide or glycopyrrolate as stated in the British National Formulary:
6.1. Chronic heart failure
6.2. Stomach ulcer
6.3. Ulcerative colitis
6.4. Significant liver disease that in the opinion of the CI or PI is a contraindication
6.5. Down's syndrome
6.6. Arrhythmia and/or history of myocardial infarction
6.7. Overactive thyroid gland.
6.8. Unstable angina
7. Current prescription for potassium chloride, digoxin, amantadine, levodopa, tricyclic antidepressants or monoamine oxidase inhibitors
8. Pregnant, trying to conceive or breastfeeding.
9. Sexually active heterosexual patients who are unable or unwilling to use contraception during the study (see section 10.4).
10. Participation in another drug study within the preceding 12 weeks (or within 5 half-lives of an IMP, whichever is longer) or use of other investigational drugs.
11. Active suicidal ideation as assessed within usual care.
12. Known sensitivity to any interventions or excipients.
13. Known history of intestinal obstruction.
14. Known history of urinary retention.
15. Severe renal impairment (eGFR <30 ml/min/1.73m2).
16. Known history of brain tumour or encephalitis.

Previous participant exclusion criteria:
1. Medical conditions that could influence hypersalivation (e.g., Parkinson's Disease).
2. Neurological conditions that could affect cognitive functioning during the course of the study (e.g., unstable epilepsy).
3. History of an allergic reaction to hyoscine hydrobromide
4. History of an allergic reaction to glycopyrrolate.

5. Any of the following contra-indications to hyoscine hydrobromide or glycopyrrolate as stated in the British National Formulary:
5.1. Prostatic enlargement
5.2. Myasthenia gravis
5.3. Pyloric stenosis
5.4. Paralytic ileus
5.5. Glaucoma
5.6. Hepatic Impairment
6. Any of the following cautions to hyoscine hydrobromide or glycopyrrolate as stated in the British National Formulary:
6.1. Chronic heart failure
6.2. Stomach ulcer
6.3. Ulcerative colitis
6.4. Significant liver disease that in the opinion of the CI or PI is a contraindication
6.5. Down's syndrome
6.6. Arrythmia and/or history of myocardial infarction
6.7. Overactive thyroid gland.
6.8. Unstable angina
7. Current prescription for a) potassium chloride, b) digoxin, c) amantadine, or d) levodopa.
8. Pregnant, trying to conceive or breastfeeding.
9. Patients who are unable or unwilling to use contraception during the study or abstain from sexual intercourse (see section 10.4).
10. Participation in another drug study within the preceding 12 weeks or use of other investigational drugs.
11. Active suicidal ideation as assessed within usual care.
12. Known sensitivity to any interventions or excipients.
13. Known history of intestinal obstruction.
14. Known history of urinary retention.
15. Severe renal impairment (eGFR <30 ml/min/1.73m2).
16. Known history of brain tumour or encephalitis.

Date of first enrolment
20/08/2024

Date of final enrolment
20/11/2027

Locations

Countries of recruitment
United Kingdom

Study participating centre
Mersey Care NHS Foundation Trust
V7 Building
Kings Business Park
Kings Drive

Prescot
United Kingdom
L34 1PJ

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

Study participating centre
Greater Manchester Mental Health NHS Foundation Trust
Prestwich Hospital
Bury New Road
Prestwich
Manchester
United Kingdom
M25 3BL

Study participating centre
Birmingham Women's NHS Foundation Trust
Birmingham Womens Hospital
Metchley Park Road
Birmingham
United Kingdom
B15 2TG

Study participating centre
Birmingham and Solihull Mental Health NHS Foundation Trust
Unit 1
50 Summer Hill Road
Birmingham
United Kingdom
B1 3RB

Study participating centre
Pennine Care NHS Foundation Trust
225 Old Street
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United Kingdom
OL6 7SR

Study participating centre
Somerset NHS Foundation Trust
Trust Management
Lydeard House
Musgrove Park Hospital
Taunton
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TA1 5DA

Sponsor information

Organisation
University of Liverpool

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Clinical Directorate, 4th Floor, Thompson Yates Building, The Quadrangle
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+44 (0)77 17 863747
sponsor@liverpool.ac.uk

Sponsor type
University/education

Website
http://www.liv.ac.uk/

ROR
https://ror.org/04xs57h96

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
Conference presentation
Publication on website
Submission to regulatory authorities
Registration on a public database

Intention to publish date
20/11/2027

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request. Requests should be made to LCTC by email to gothic2@liverpool.ac.uk

At the end of the trial, after the primary results have been published, the individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank CRF) will be prepared in order to be shared with external researchers.

IPD will only be shared with external researchers if the participants have consented to this onward disclosure in accordance with the Common Law Duty of Confidentiality, or if the external researchers obtain approval to waive this Common Law requirement (i.e. Section 251 Approval via the Confidentiality Advisory Group (CAG) / approval from the Public Benefit & Privacy Panel for Health & Social Care (PBPP)) or if the IPD has been fully anonymised prior to sharing.

All requests for access to the IPD will be assessed by the Sponsor and must be agreed by all Data Controller organisations. If a request is approved, it will be processed by LCTC.

IPD sharing plan summary
Available on request