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Evaluating the safety of acute baclofen in methadone-maintained individuals with opiate dependence. (FORWARDS-1)

Submission date
15/08/2023

Recruitment status
No longer recruiting

Registration date
22/08/2023

Overall study status
Completed

Last Edited
24/11/2023

Condition category
Other

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

Plain English summary of protocol

Background and study aims
Opiate addiction is a big problem for people's health. One common treatment is to replace the addictive substance with a safer one, like using methadone instead of opiates. But many want to completely stop using these substances. For older people with more complicated health issues, quitting the addiction might be better.
When trying to quit, the usual method is to gradually reduce the use of the safer substance while using other medications to deal with the symptoms that come up. However, these medications might not always work well or be good for long-term use. So, new treatments are needed.
Researchers think that a medication called baclofen could help with this. Baclofen is used to treat muscle problems and alcohol addiction. There's some evidence that it might work for opiate addiction too. It could help with common withdrawal symptoms like trouble sleeping, anxiety, and restless legs.
The researchers have seen in their own experience and from other studies that baclofen might be safe to use with methadone (the safer substance). But there's a chance that using both together might cause problems like breathing issues. They also want to make sure that baclofen doesn't become addictive when used this way.
So, the goal of this study is to find out the right amounts of baclofen and methadone that can be used together safely. They also want to check if people start to like baclofen too much when they use it.

Who can participate?
Patients (over 21 years old) engaged in treatment for opiate dependence from community addiction services and receiving stable doses of OST with methadone will be invited to undergo screening at the Imperial Clinical Research Facility (ICRF) at Hammersmith hospital, or at their local addiction clinic.

What does the study involve?
Eligible participants will attend the ICRF for their experimental visit (one day). They will take their usual dose of methadone followed 40-60mins later by either placebo or baclofen. This is a

single-blind trial, therefore the participants will not be aware of whether they are taking placebo or baclofen tablets. Acute baclofen (10mg, 30mg, 90mg) or placebo will be orally administered (randomised, single-blind, 3:1 ratio respectively) with the dose determined by a Bayesian adaptive trial algorithm. The effects of baclofen or placebo will be monitored for up to 5 hours following dosing. A range of measures will be taken during that time including: respiration (eg number of breaths/minute, oxygen and carbon dioxide levels), cardiovascular (pulse, blood pressure, QTc), sedation as well as mood and drug effects including drug liking, anxiety and craving. When possible blood samples will be taken to assess plasma concentrations of baclofen, methadone and growth hormone (index of GABA-B function). Participants will go home in a taxi at the end of the day. They will be called the following morning to see how they are, if they have experienced any adverse events and about sleep, and restless legs. The study duration will be ~2-3 weeks from pre-screening phone call to the post visit follow up phone call.

What are the possible benefits and risks of participating?
Research participants will not directly benefit from taking part but the information we get might help improve the treatment of people with opiate dependence in future. Participants will receive feedback if requested about all aspects of the study, but this will not be available until the end of the study as this is a research investigation and the clinical relevance of the measures taken is not proven. All opiate dependent participants will be engaged with a specialist clinical service and will therefore be receiving support and know how to access extra support if required. This will reduce the risk of participant's use of on-top drugs eg heroin, crack cocaine. This risk will be further attenuated by careful screening by an experienced research team. We will monitor for any signs of respiratory depression and such information will be utilised in the model to determine the next safe dose combination. We have enhanced assessments of possible respiratory impairment in our screening protocol so that anyone at risk of respiratory depression is excluded. In a previous similar study in alcoholism, participants reported minor side effects to the 60mg dose of baclofen, primarily dizziness and, nausea. These side effects however resolved and all participants were fit to be discharged by end of the study day. Some participants may find the long experimental study day tiring. We will endeavour to take all steps to ensure comfort and provide appropriate rest and sustenance during these procedures.

Where is the study run from?
Participants will be recruited from Addiction services in northwest London delivered by the following organisations: Central North West London NHS Foundation Trust, CGL. The experimental day will be conducted in the Imperial Clinical Research Facility at Hammersmith hospital.

When is the study starting and how long is it expected to run for?
July 2021 to November 2022

Who is funding the study?
Medical Research Council (UK) MR/T025557/1

Who is the main contact?
Prof Anne Lingford-Hughes, anne.lingford-hughes@imperial.ac.uk

Contact information

Type(s)
Principal investigator

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05161351

Clinical Trials Information System (CTIS)
2021-002556-36

Integrated Research Application System (IRAS)
1003802

Central Portfolio Management System (CPMS)
50650

Protocol serial number
21HH6830

Study information

Scientific Title
Evaluating the safety of acute baclofen in methadone-maintained individuals with opiate dependence. An adaptive, singleblind, placebo-controlled ascending dose study of acute baclofen on safety parameters in opioid dependence during methadone-maintenance treatment; a pharmacokinetic-pharmacodynamic study. (FORWARDS-1)

Acronym
FORWARDS-1

Study objectives
1. CNS depressant activity:
1.1. We anticipate no evidence of clinically significant respiratory depression or cardiovascular changes in doses up to 90mg baclofen in those on daily methadone doses up to and including 120mg.
1.2. We hypothesise that we will observe increased self-reported measures of drug effect,

including sedation, with doses at or above 60mg baclofen relative to placebo, in combination with methadone doses at or above 60mg.
• Increased T-SHAS drug effect score relative to placebo, at peak effect (2-3 h following dosing).
• We hypothesise that signs of sedation in this opiate dependent cohort will be blunted in response to baclofen as compared with historic controls (Durant et al., 2018).
• Reduced peak subjective response following baclofen administration at doses of 60mg or above.
2. Abuse liability:
2.1. We hypothesise that we will observe no indication of abuse liability of baclofen relative to placebo in combination with methadone.
• No clinically meaningful change from placebo in DEQ 'liking' or 'want more' subscales.
3. PK-PD measures:
3.1. We anticipate that opiate dependent individuals will demonstrate lower sensitivity to baclofen as compared with historic controls, as follows:
• Reduced growth hormone response relative to controls at peak effect (~2h post dose) following 60mg baclofen
• Reduced sedation response (self-report measures) relative to controls at peak effect (2-3h post dose) following 60mg baclofen
3.2. We anticipate that opiate dependent participants will demonstrate a comparable pharmacokinetic profile in response to baclofen as compared with healthy controls and those with alcohol dependence (data from (Durant et al., 2018))
4. We expect that baclofen will reduce anxiety after acute dosing and improve sleep measures during the subsequent night of sleep, compared with placebo.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 23/07/2021, West of Scotland REC 1 Research Ethics Committee (West of Scotland Research Ethics Service, Ward 11 Dykebar Hospital, Grahamston Road, Paisley, Glasgow, PA2 7DE, United Kingdom; +44 141 314 0212; WosRec1@ggc.scot.nhs.uk), ref: 21/WS/0080 1003802

Primary study design
Interventional

Study design
Single-blind adaptive randomized placebo-controlled ascending dose study

Study type(s)
Safety

Health condition(s) or problem(s) studied
Opiate dependence

Interventions
Participants will be randomised in a 3:1 ratio to baclofen or placebo. Participants allocated to baclofen will be dosed in groups of up to 3, with a maximum available sample size of 64 (up to 48 on baclofen and 16 on placebo). An adaptive model will inform the dosage of baclofen for each patient group based on the trial data accumulated to date.

The ‘treatment’ was a single challenge in the morning of baclofen or placebo. There was a phone call the following morning. The total duration was ~24hrs.

Randomisation was determined by the model which told us whether the next participant was to receive baclofen or placebo and at what dose.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Baclofen, placebo (vitamin D)

Primary outcome(s)
The maximum safe dose of baclofen at which 15-25% of evaluable participants experience a dose limiting toxicity (DLT) for prescribed doses of methadone, where a DLT is comprised of the following components:
1. Intervention level (0 to 4)
2. National Early Warning Score (NEWS2), measured at discrete time-points
3. Glasgow Coma Scale (GCS) score, measured at discrete time-points
4. QTc on ECG trace, measured at discrete time-points
5. Measures of respiratory function, measured continuously at discrete time-points
5.1. Oxygen saturation (SPO2)
5.2. Respiratory (ventilation) rate
5.3. Incidence of apnoea.

Dose Limiting Toxicity (DLT) is defined as:
1. Situation requiring intervention level ≥4 at any time
2. NEWS2 score >4 or score of 3 in any parameter (threshold for trigger of urgent ward-based response)
3. Measures of respiration with a persistent change in at least one of:
3.1. Reduction in SPO2 [≤91% for more than 30 seconds or >5% reduction in SpO2 for more than 30 seconds
3.2. Reduced respiratory rate (≤8/min)
3.3. Absence of inspiratory airflow for >30s combined with a sustained fall in SpO2
4. GCS score <12
5. Persistent QTc prolongation (>500ms or increase of >60ms; if the initial QTc value at any time-point is prolonged, the ECG should be repeated two more times- with 5 minutes between ECG readings- and the average of the 3 QTc values used to determine DLT).

Key secondary outcome(s)
1. Respiratory measures:
These will be investigated at each baclofen dose level, for signs of sub-threshold respiratory depression.
1.1. SpO2- instances of <92% or of >5% reduction for more than 10 seconds
1.2. CO2- instances of ETCO2% per breath exceeding 6.5% (Jolley et al., 2015) or a partial pressure CO2 increase by 1kPa (advice from respiratory physician)
1.3. Respiratory rate- instances of absence of inspiratory airflow for more than 10 seconds or respiratory rate drops <9/min

1.4. Time course of SpO2, CO2 and respiratory rate following baclofen dosing, relative to placebo.
2. Sedation measures:
2.1. T-SHAS score (total score on Subjective High Assessment Scale)
2.1.1. Mean Total-SHAS score at peak PD response (2-3h) at each baclofen dose level, relative to placebo
2.1.2. Time-course of T-SHAS at each baclofen dose level, relative to placebo
3. Symptom measures:
3.1. Drug Effects Questionnaire (DEQ)
3.1.1. Mean 'Drug liking' and 'want more' scores at peak PD response (2-3h) at each baclofen dose level, relative to placebo
3.1.2. Time-course of DEQ scale at each baclofen dose level, relative to placebo

Completion date
11/11/2022

Eligibility

Key inclusion criteria
1. Male or female
2. Aged over 21 years
3. Willing and able to comply with protocol
4. Able to read, comprehend and record information written in English
5. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
6. Healthy as determined by a responsible physician, based on a medical evaluation which includes medical history, a physical examination, laboratory tests (if required), and a psychiatric evaluation. A volunteer with clinical parameters outside the reference range for the population being studied may be included, only if the investigators concur that the finding is unlikely to jeopardize either subject safety or study integrity.
7. DSM-5 diagnosis of current severe opioid use disorder
8. Treated with methadone substitution therapy and able to maintain the same stable dose for screening and experimental visit.
9. Ability to receive an acute dose of up to 90mg baclofen or up to 4800IU vitamin D (placebo).

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
21 Years

Sex
All

Total final enrolment

Key exclusion criteria

1. Intoxication on any of the visits, as assessed by difficulty in walking, the slurring of speech, difficulty concentrating or drowsiness. This exclusion criteria would exclude a subject from that study day only and not the whole study, at the discretion of the research team.
2. Positive urine drug screens or breath alcohol at screening or experimental testing visits. A minimum list of drugs that will be screened for include amphetamines, cocaine, opiates, methadone, cannabinoids and benzodiazepines. Positive results for methadone will be allowed for those opiate dependent participants still undergoing OST. Positive results for cannabinoids will be allowed given the long half-life of cannabinoid metabolites. This exclusion criteria would exclude a subject from that study day only and not the whole study, at the discretion of the research team.
3. Current DSM-5 substance dependence disorder for any other substance except for opiates and nicotine. Lifetime history of dependence on other substances will be allowed given very high incidence of co-dependence.
4. Regular on-top use of heroin or other opiates or other illicit substances in combination with OST, which in the opinion of the investigators will interfere with subject safety or study integrity.
5. Any participant taking over 120mg/day of prescribed methadone.
6. Current severe DSM-5 mental health disorder (excluding opiate dependence). Current moderate or mild DSM-5 depressive, anxiety, sleep or personality disorders will be allowed given the high levels of comorbidity, provided in the opinion of the investigators, the participant is able to complete study procedures satisfactorily..
7. Current or past history of enduring severe mental illness e.g. psychotic disorder (excluding drug induced), schizophrenia, bipolar affective disorder).
8. Active suicidality.
9. Use of regular prescription medications which in the opinion of the investigators will interfere with subject safety or study integrity. Regular use of psychotropic medication will be permitted e.g. antidepressants, provided the participant is compliant with administration and the investigators concur that they will not interfere with subject safety or study integrity.
10. Participants are taking any medication that is contraindicated with baclofen or placebo (vitamin D3), or are hypersensitive to them or any of their excipients.
11. Participants that are taking any medication that in the opinion of the investigators may impact on the outcome measures during the experimental session.
12. Use of intermittent psychotropic medication which in the opinion of the investigators will interfere with subject safety or study integrity.
13. End stage or acute renal failure.
14. Severe chronic obstructive pulmonary disease (COPD) or Type 2 respiratory failure.
15. Pulse rate <40 or >100 BPM OR systolic blood pressure >160 and <100 and a diastolic blood pressure >95 and <60 in the semi-supine position.
16. Oxygen saturation <92% at rest
17. A screening ECG with a QTcB or QTcF > 500 msec or an ECG that is not suitable for QT measurements (e.g. poorly defined termination of the T-wave) and/or with another ECG abnormality which in the opinion of the study physician is clinically significant and represents a safety risk. Note that if the initial QTc value is prolonged, the ECG should be repeated two more times (with 5 minutes between ECG readings) and the average of the 3 QTc values used to determine eligibility.
18. Clinically significant head injury (e.g., requiring medical or surgical intervention) that in the opinion of the investigators, contraindicates their participation .
19. Active hepatitis or HIV.
20. Active peptic ulceration.

21. Significant current or past medical history that, in the opinion of the investigators, contraindicates their participation.
22. The subject has participated in a clinical trial and has received an investigational product within 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer) prior to the first experimental visit.
23. Pregnancy or breast-feeding
24. Unwillingness or inability to follow the procedures outlined in the protocol

Date of first enrolment
11/01/2022

Date of final enrolment
10/11/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
CNWL NHS Foundation Trust
Addiction Services based in Brent, Ealing, Hillingdon, Hounslow Addiction services
London
United Kingdom
NW1 3AX

Study participating centre
NIHR Imperial Clinical Research Facility
Hammersmith Hospital
Du Cane Rd
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United Kingdom
W12 0HS

Sponsor information

Organisation
Imperial College London

ROR

https://ror.org/041kmwe10

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The study team will retain the exclusive use of data until the publication of major outputs has been completed. After this, data access including the full protocol, statistical codes, and participant-level data will be made available upon reasonable request to the CI, in accordance with the Data Protection Act.
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IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		18/10/2022	16/08/2023	Yes	No
Basic results			24/11/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes