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Facilitating detoxification and dose reduction from methadone using baclofen

Submission date	Recruitment status	[X] Prospectively registered
04/04/2023	Recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
31/01/2024	Ongoing	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
09/06/2025	Mental and Behavioural Disorders	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Opioid addiction remains a major challenge in the UK. Opioid substitution therapy (OST), usually methadone, is associated with reduced illicit heroin use and health improvements. When someone desires abstinence, their methadone dose is gradually reduced over weeks to reduce the risk of withdrawal symptoms. However, many find 'detoxification' difficult to tolerate due to sleep disturbance, anxiety and fear of experiencing withdrawal. These symptoms can be eased with medications, such as lofexidine, but it is no longer available in the UK so new treatments are needed.
Evidence suggests that a GABA-B agonist, baclofen, may be helpful in reducing opiate withdrawal symptoms. Baclofen is a licensed medication to treat muscle spasms. The FORWARDS-1 study established that individuals on methadone (up to 70 mg/day) could safely take 60 mg of baclofen. This study is investigating whether baclofen can help people reduce or stop their methadone.

Who can participate?
Opioid-dependent participants who wish to undergo dose reduction or detoxification from methadone

What does the study involve?
Participants will be randomly allocated to receive baclofen or placebo, alongside the usual treatment. The baclofen dose will be increased over 7-10 days to achieve a maintenance dose of 30-60 mg/day for up to 12 weeks. Participants will attend regular in-person visits and complete weekly brief questionnaires about how they are feeling while taking the study medication. Methadone dose, medication compliance, side effects and feasibility measures will be recorded at each visit. After 12 weeks every participant will have their study medication withdrawn over 7-14 days and then complete an exit questionnaire about their experience of the trial. With consent, we will contact them 3 months later to see how they are. If the trial is shown to be feasible and baclofen shows promise as a medication to assist detoxification or dose reduction, we will design a full trial to test its effectiveness.

What are the possible benefits and risks of participating?
Participants may benefit from taking part by achieving methadone dose reduction or abstinence

from methadone. The results of the study may help improve the treatment of people with opiate dependence in future.
All opiate-dependent participants will be under the care of a specialist clinical service for addictions, and therefore be receiving support and know how to access extra support if required. In order to undergo detoxification or dose reduction from their methadone, individuals must be engaged with such a service, often attending appointments regularly for many months and receiving psychosocial support, generally not using or very limited on-top use of heroin or other drugs and have a stable and supportive living situation. With the individual, the clinical team will make the decision if detoxification/dose reduction is appropriate. This will reduce any potential risk (e.g. relapse) of an individual starting before they are ready as the service will know the individual well.
The clinical teams identifying potential participants will be in close contact with the research team at Imperial College if there are any concerns about participants' suitability to take part in the study or any changes in circumstances post-screening.
No treatment is withheld from participants in this study, as the addition of baclofen or placebo is an adjunct to treatment as usual, and they remain on their dose of methadone until such time as their treating psychiatrist/doctor deems it appropriate to adjust their dose.
Participants will be regularly asked about their physical and mental health during the study. The baseline interview will include questions on personal history, substance use and recovery plans. This may bring up sensitive or triggering issues, but they are relevant to any study of drug dependence. The local addiction service where the interviews will take place will be able to provide support and guidance to help reduce any concerns.
Individuals in treatment are regularly asked about how they are feeling and any difficulties they may be experiencing. The lengthier questionnaires will take place in clinic or over the phone with their key worker or member of the research staff who will be able to offer advice or support or direct them to access appropriate support as required. Online questionnaires completed at their convenience will be much shorter and will include a reminder to contact their local service if they need any support or assistance.
The GABA-B receptor agonist, baclofen, is a licensed medication with a very good tolerability and safety profile. The dose used in this study (up to 20 mg tds) is lower than the usual dose prescribed for spasticity (100 mg) and is commensurate with that used to treat alcoholism. From our clinical and research experience with baclofen, we do not experience any issues from this dose. To mitigate any side effects, why participants are advised to take their baclofen or placebo three times a day, with meals, to reduce the impact of this.
The SmPC raises the issue of potential misuse, abuse and dependence for baclofen. We are aware of this and are monitoring participants regularly during the trial including measures of medication compliance, adherence and subjective effects, and participants and staff have access to a 24-hour phone line to seek advice and to report any issues. Participants also receive care and support from their clinical addiction service which is experienced in identifying, assessing and managing such issues.
As baclofen is not routinely prescribed to this particular patient population or administered alongside opiate substitute medication there are specific considerations. In the preceding FORWARDS-1 trial (completed December 2022) we established it is safe to co-prescribe doses of up to 70mg methadone per day with up to 60 mg baclofen so we believe these risks are low due to clinical experience and previous studies. Baclofen is not contraindicated in hepatitis C or liver dysfunction that may be present in opiate addicts.
As with all such clinical trials there are safety risks, but they will be minimised as much as possible by obtaining safety parameters around combination use and instructing clinicians to use a pragmatic approach to dosing in the trial, and using well-trained staff and adherence to established safety protocols and SOPs.

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
March 2023 to December 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Louise Paterson, l.paterson@imperial.ac.uk

Study website
https://www.imperial.ac.uk/brain-sciences/research/psychiatry/forwards-2/

Contact information

Type(s)
Public, Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1007293

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
23IC8233, CPMS 59093, IRAS 1007293

Study information

Scientific Title
Facilitating opiate recovery: withdrawal and abstinence through detoxification support

Acronym
FORWARDS-2

Study objectives
The primary aim of this study is to establish proof-of-concept as to whether baclofen can facilitate a successful reduction in methadone dose during detoxification in opioid dependence. The primary objective is to determine whether there is superiority of baclofen as compared with placebo.

Secondary objectives include:
1. Learning whether participants achieve successful abstinence at or prior to the 12-week timepoint
2. Whether measures of acceptability of the treatment, retention in detoxification treatment, tolerability and medication compliance are acceptable
3. Whether there is any indication of improvement in other clinical markers including anxiety, craving, sleep, restless legs and other substance use

The feasibility aspect of this trial aims to determine whether the proposed recruitment rate is achievable and whether retention rates are favourable, as measured by the number of participants randomised, and the retention rate at 12 weeks.

Exploratory and qualitative objectives will determine sample characteristics, explore barriers to detoxification and treatment expectations, and determine whether participants remain abstinent or at their reduced methadone dose for up to 3 months after completing the study.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/10/2023, West of Scotland REC1 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, UK; +44 (0)141 314 0212; WoSREC1@ggc.scot.nhs.uk), ref: 23/WS/0064

Study design
Randomized placebo-controlled double-blind parallel-group trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Community

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Opioid dependency

Interventions
Intervention arm: after randomisation, which will take place using Sealed Envelope within OpenClinica, participants will be titrated up to a minimum of 10 mg baclofen TID, to be taken orally, up to a maximum of 20 mg TID over a period of 7-12 days. Study medication will be taken in addition to the prescribed methadone dose, for up to 12 weeks, or less if abstinence is achieved earlier. During this time participants will complete weekly follow-up questionnaires and attend in-person visits every three weeks. At the end of the study, participants will be tapered off baclofen over a period of 7-10 days, attend an exit visit and provide follow-up data on methadone dose for up to 3 months following trial exit.

Control arm: after randomisation, which will take place using Sealed Envelope within OpenClinica, participants will be titrated up to a minimum of three placebo tablets TID, to be taken orally, up to a maximum of six placebo tablets TID over a period of 7-12 days. Study medication will be taken in addition to the prescribed methadone dose, for up to 12 weeks, or less if abstinence is achieved earlier. During this time participants will complete weekly follow-up questionnaires and attend in-person visits every 3 weeks. At the end of the study, participants will be tapered off placebo over a period of 7-10 days, attend an exit visit and provide follow-up data on methadone dose for up to 3 months following trial exit.

Intervention Type
Drug

Phase
Phase IV

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

Primary outcome measure

Reduction in methadone dose with baclofen compared with placebo at 12 weeks, or time of abstinence if sooner. The difference in methadone dose will be measured by calculating the difference in methadone dose (in mg) at baseline compared with 12 weeks (or time of abstinence).

Secondary outcome measures

1. Successful abstinence, defined as the first instance of a reduction in methadone dose to 0 mg for 3 or more days between initiation of study treatment and the end of the 12-week maintenance period
2. Time to successful abstinence measured between initiation of study treatment and the first instance of a reduction in methadone dose to 0 mg for 3 or more days up to the end of the 12-week maintenance period
3. Days of abstinence from methadone between initiation of study treatment and the end of the 12-week maintenance phase or until time of successful abstinence if earlier, measured using the total number of days 0 mg methadone taken as reported by patients using electronic data capture (ePRO).
4. Number of methadone dose changes from initiation of study treatment up to end of the 12-week maintenance period or until time of successful abstinence if earlier, as measured by (i) patient report and (ii) prescribing service.
5. Methadone dose regardless of any period of abstinence, measured using prescribed methadone dose at Week 12, extracted from clinical records
6. Maximum baclofen/placebo dose administered during the 12-week maintenance phase or from the start of the maintenance phase to the time of successful abstinence if earlier, as measured by (i) patient report and (ii) prescribing service.
7. Proportion of time over the 12-week maintenance phase or from the start of the maintenance phase till the time of successful abstinence if earlier at (a) minimum target dose of baclofen /placebo (10 mg tds) and (b) maximum target dose (20 mg tds) as measured by (i) patient report and (ii) prescribing service.
8. Patient rating of psychological health, physical health and overall quality of life in last 7 days at 12 weeks or time of successful abstinence if earlier, measured using the Treatment Outcomes Profile (TOP)
9. Patient rating of craving, measured using 0 to 100 visual analogues scales (VAS-Need and VAS-Want) for heroin and cocaine in the last 7 days at 12 weeks or time of successful abstinence if earlier
10. Patient rating of anxiety, withdrawal, sleep disturbance, and restless legs symptoms in the last 7 days, measured using 0 to 10 Likert scales at 12 weeks or time of successful abstinence if earlier
11. Patient rating of drug effect ‘liking’ and ‘want more’ over last 7 days, measured using a 0 to 10 Likert scale at 12 weeks or time of successful abstinence if earlier
12. Total number of days using heroin during the 12-week maintenance phase or from the start of the maintenance phase till the time of successful abstinence if earlier, measured using the Treatment Outcomes Profile (TOP)
13. Total number of days using other substances (e.g. alcohol, nicotine, cocaine, etc) during the 12-week maintenance phase or from the start of the maintenance phase till the time of successful abstinence if earlier, measured using the Treatment Outcomes Profile (TOP)
14. Total number of days abstinent from all illicit substances during the 12-week maintenance phase or from the start of the maintenance phase till the time of successful abstinence if earlier, measured using the Treatment Outcomes Profile (TOP)
15. Total number of days abstinent from all substance use during the 12-week maintenance phase or from the start of the maintenance phase till the time of successful abstinence if earlier, measured using the Treatment Outcomes Profile (TOP)

16. The number of days using heroin in the last 28 days at 12 weeks or time of successful abstinence if earlier, measured using the Treatment Outcomes Profile (TOP)
17. The number of days using other substances (e.g. alcohol, cocaine, smoking cigarettes/e-cigarettes, etc) in the last 28 days at 12 weeks or time of successful abstinence if earlier, measured using the Treatment Outcomes Profile (TOP)
18. Score for Opioid Use Disorder (OUD) severity (PRO-S; baseline) and improvement (PRO-I) measured at 12 weeks or time of successful abstinence if earlier
19. Score for Clinical Opiate Withdrawal Scale (COWS) at 12 weeks or time of successful abstinence if earlier
20. Number of baclofen/placebo dose changes during the 12-week maintenance phase or from the start of the maintenance phase to the time of successful abstinence if earlier, as measured by (i) patient report and (ii) prescribing service

Overall study start date
30/03/2023

Completion date
31/12/2025

Eligibility

Key inclusion criteria
1. Classified or determined by their addiction service as ready for dose reduction or detox
2. >18 years old
3. Current or previous DSM-5 moderate to severe opioid use disorder or ICD10/11 opioid dependence
4. Currently treated with methadone substitution therapy
5. The client wishes to undergo methadone detoxification and/or dose reduction

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
112

Key exclusion criteria
1. Lack of capacity to consent
2. Unable to take oral medication
3. Contraindication for baclofen, as per SmPC guidance
4. History of allergic or adverse reactions to baclofen, or placebo, or any of their excipients
5. Where there are "Special warnings and precautions for us" according to the SmPC AND where

the risk vs benefit ratio for prescribing is not in favour of prescribing medication (see SmPC)
6. Current and ongoing substance dependence (including alcohol), except for opiates and nicotine, with no desire to stop at this time
7. Clinician does not deem that the individual is suitable to undergo dose reduction or detoxification from methadone at this time
8. Use of regular prescription or illicit medications or drugs which in the opinion of the investigators will interfere with subject safety or study integrity
9. Severe chronic obstructive pulmonary disease or Type 2 respiratory failure
10. Unable to follow the study protocol due to serious mental health disorder e.g. enduring psychotic illness, suicidal intent
11. Any woman who is pregnant, of child-bearing potential refusing a pregnancy test or unwilling to use adequate contraception for the duration of the trial

Date of first enrolment
05/02/2024

Date of final enrolment
31/10/2025

Locations

Countries of recruitment
United Kingdom

Study participating centre
Not provided at time of registration
United Kingdom
-

Sponsor information

Organisation
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Sponsor type

University/education

Website
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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, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website
5. Other publication
6. Submission to regulatory authorities

Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators. No identifiable information will be shared. Publications will be made available in the public domain. 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.

Intention to publish date
30/11/2025

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

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