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Suboxone treatment and recovery trial

Submission date
15/11/2015

Recruitment status
No longer recruiting

Registration date
07/08/2016

Overall study status
Completed

Last Edited
12/08/2022

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
Opioids are a type of drug that is often used as painkillers. They work by reducing the number of pain signals that the body sends to the brain and changes how the brain responds to the pain. Opioid drugs include heroin, morphine, codeine and tramadol. Opioids are safe when used correctly, but people who take them inappropriately – that is taking them in a way other than following a doctors instructions - can become addicted to them. Addiction is a disease that affects a person's brain and their behaviour. Over time, the brain changes in such a way that an affected individual develops a powerful urge to use the drug all the time. In this study, patients with addiction to heroin, morphine or prescription opioids will be treated using an approved treatment that reduces the intensity of the symptoms that happens when people suddenly stop taking the drugs – in other words, it helps to ease the withdrawal symptoms. The treatment also reduces the urge to use the drugs and increase the resistance to the effects of the drug if used while on treatment. This treatment is called Suboxone and is available as a film that is dissolved if placed on the tongue. The study is in two parts. The first involves an inpatient stay of 4 weeks where patients will be stabilised on the doses that eliminates or reduces the urge and discomfort to the minimum. During this phase 4 blood samples will be withdrawn from the patients. After completing this phase, patients are discharged to the outpatient clinic where they are randomly assigned to be in a group that receives extended take home doses based on their 1) level of substance use, 2) clinic attendance and 3) taking medication as prescribed supported by a random and scheduled blood test. The second group receives take home doses without the preceding frame work. The duration of follow up period at the outpatient clinic is a total of 16 weeks.

Who can participate?
Adults between 18-65 year of age using opioids, diagnosed with a Opioid Use Disorder, and admitted to treatment at the National Rehabilitation Center.

What does the study involve?
Patients recruited for the study are admitted to an inpatient treatment starting with a 3-5 days detoxification using suboxone which is compared to two active medications, Buprenorphine and Naloxone. This phase is followed by an early recovery phase for a total period of up to 4 weeks. During this phase the patient undergoes a number of tests to check how addicted they are and also their mental wellbeing. These assessments are completed via an interview using a structured questionnaire and a set of simple questionnaires that can be completed by the

patient. The patient is also stabilized on what is called the optimal dose of suboxone. This dose is the one that achieves minimal or no craving and prevents withdrawal symptoms. Depending on the patient needs, the dose can be either daily, every other day or three times a week. The patient provides 4 blood samples after remaining on the same dose of suboxone for at least 14 days. Once completed the patient is prepared for discharge and is randomly allocated to either a group that receives treatment as usual or that receives counseling and medication adjustments and monitoring

What are the possible benefits and risks of participating?
Participants will not experience more than the usual level of risk associated with treatment as usual and may be treated longer under this study achieving a better result.

Where is the study run from?
The National Rehabilitation Center, Abu Dhabi (United Arab Emirates)

When is study starting and how long is it expected to run for?
January 2014 to January 2017

Who is the main contact?
Dr Hesham Elarabi

Contact information

Type(s)
Scientific

Contact name
Dr Hesham Elarabi

Contact details
King’s College London
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SE5 8AF

Additional identifiers

Protocol serial number
2014/2/NRC

Study information

Scientific Title
Optimizing opioid assisted therapy : personalizing treatment using therapeutic drug monitoring and medication management

Acronym
START

Study objectives
START will evaluate the following three main (non-directional) hypotheses:
1. There will be no difference in:
1.1. The rate of UDS (urine drug screening) morphine negative tests
1.2. Treatment retention
1.3. Indicators of psychological and social functioning between medication assisted treatment using BNX-F (buprenorphine-naloxone film) plus TDM (therapeutic drug monitoring) and MAP compared to BNX-F only
2. There will be no difference in:
2.1. The rate of UDS morphine negative tests
2.2. Treatment retention
2.3. Indicators of psychological and social functioning between patients receiving three-times per week, alternate day and daily dosing of BNX-F
3. There will be no difference in:
3.1. The rate of UDS morphine negative tests
3.2. Treatment retention
3.3. Indicators of psychological and social functioning among patients contrasted on demographic, neuro- and molecular biological factors.
4. There will be no difference between accuracy of assigning doses based on clinical prediction or randomly assessed by adjustment of doses for more than 40% of the participants.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Health Authority of Abu Dhabi Licensed Internal Review Board of the National Rehabilitation Center

Study design
Single-centre, phase-IV randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Opioid use disorders (prescription opioids and illicit opiates)

Interventions
Inpatient phase (4 weeks):
Participants using illicit opioid dependence will receive a 3-day BNX-F dose induction; those using prescription opioid use will receive a 5-day induction. This is followed by a 14-day dose stabilisation (patients allocated to daily, alternate day or thrice weekly dosing regimens) according to the pre-set allocation criteria (Clinical Assignment decision rule). Adverse events will be addressed according to defined interventions. All medication administration during the in-patient phase will be directly observed dosing (DOT). Buprenorphine and Non-buprenorphine concentrations are assayed at the NRC Laboratory by Liquid Chromatography Mass Spectrophotometry (LC-MS). With each patient expected to have a different steady state and

concentration time curve, the objective is to establish a BUP steady state over 14 doses. This will be achieved for each patient by:
1. Examination of the patient's maximum plasma concentration [C-max]
2. The trough levels measured 30 minutes before the next dose
3. Calculation of their elimination rate constant (i.e. the slope of the drug concentration-time curve) via comparison of the BUP and non-buprenorphine concentrations) and verification of the end rate constant (to confirm that the end rate elimination rate constant has not changed significantly from the calculated rate constant for the non-daily doses). Once established, a patient's observed Steady State Concentration (SSC) is compared with the expected SSC concentration calculated. A criterion for adherence for the subsequent outpatient phase was set as a 10% deviation range from the SSC5

Procedure:
Clinical assignment decision rule. During the inpatient phase, participants are assigned to daily, alternate day or thrice weekly dosing schedules according to the following assignment process developed at the NRC:
1. those injecting street heroin and morphine receive daily doses
2. oral street heroin and morphine users receive alternate daily doses
3. those using prescription opioids receive thrice weekly doses. In addition, patients with severe psychiatric co-morbidity, or multiple substance use, or with a Body-Mass Index greater than or equal to 30 are placed on the next higher frequent dosing schedule. Dose guided by self-report and pupil diameter measurement is done every three days.

Randomisation procedure:
At completion of the in-patient phase, participants will be allocated to the experimental or control conditions on a 1:1 basis and stratified by primary opioid (i.e. heroin or other non-medical pharmaceutical opioid); BNX-F dosing interval (i.e. daily; alternate day; or thrice weekly); and home locality (Abu Dhabi metropolitan area or elsewhere in UAE). The randomization procedure will be implemented in the NRC's inpatient setting prior to discharge to the outpatient programme. An online randomisation protocol will be used [26] and administered independently.

Intervention:
Experimental condition participants receive a 16-week outpatient BNX-F treatment programme TDM and medication management support, as follows:
1. BNX-F. After randomization participants will continue treatment in the outpatient setting for 16 weeks. An initial 1-week phase will require participants to attend the clinic according to their assigned dosing schedule (i.e. daily, on alternate days or three times) for directly observed dosing and to provide (randomly) a minimum of three urine samples for drug toxicology screening. If the patient does not attend the clinic or if the urine sample is positive for opioid use, they continue on DOT. Those who provide a negative drug test at their last visit in the first week are given a one week take home prescription. If positive the patient is returned to DOT, or placed on two weeks take home doses if negative and the process is repeated for three weeks take home doses till a maximum of 4 weeks. The patient will be advised to not take their BNX-F dose on the follow up visit day and quantity dispensed for scheduled visits will account for that. The anticipated concentration for this sample will then be compared with assay results. Non-adherent or non-abstinent patients will be pushed down one level on their take home doses. For example if the patient is on three weeks take home doses and was found non-compliant as per the TDM results or provided a random positive UDS he is brought down to two weeks take home doses instead of extending take home to four weeks, and from two weeks to one week and then DoT thereafter.
2. TDM: Between scheduled visits, patients on three week take home doses and longer are randomly called for blood sample BUP assay. Compliant patients will receive 4 weeks take home

doses at scheduled follow up visit and no blood will be drawn for TDM on that visit. Each patient is to receive a minimum of 3 random TDM during the 16 week follow up period without increasing the total number of assays and number of whole blood samples drawn.
Starting from the three week take home dose duration and upwards, the patient is randomly called once during the take home dose period to provide a urine sample for testing and a blood sample for TDM. The TDM results will enable the study classify the participant into one of four categories (with planned response actions), as follows:
2.1. Abstinent and adherent. Response: A discussion is held to reinforce and motivate continued abstinence and medication adherence.
2.2. Abstinent but non-adherent. Response: A discussion is held to reinforce and motivate continued abstinence but remind patient about the value of adherence, identify the source of non-adherence and strategies to improve adherence, arrange for a follow up call on the agreed tasks, and 'step down' take home dose periods.
2.3. Non-abstinent but adherent. Response: reinforce and motivate continued medication adherence; but remind patient about the value of abstinence; assess the context, triggers for using and discuss relapse prevention strategies; assess co-morbid conditions and social situation.
2.4. Non-abstinent and non-adherent. Response: assess relapse/lapse, response to medication including cravings, refer to psychology and social work as required, step down take home dose periods, explore the involvement of family members and close network, step down take home doses
2.5. Medication management. Adapted from a protocol for addiction pharmacotherapy research by a US trial of alcohol pharmacotherapy and a US manual for opioid agonist pharmacotherapy patients will be invited to participate in a 16-week medication management programme. The aim is to help and support patients to set their own recovery goals and:

2.5.1. Understand the importance of taking BNX-F as prescribed and incorporating this into their day-to-day activities
2.5.2. Be aware of the action of BNX-F and how to monitor for opioid withdrawal symptoms and side-effects
2.5.3. Recognize and cope with cravings to use opioids and lapses to opioid and other drug use; (4) build and sustain motivation for abstinence and the supports and recovery assets

The 16-week medication management protocol comprises six individual sessions (approximately two hours in total) with a member of the START clinical team, as follows:
2.5.4. A foundation session scheduled on the first working day following discharge (Week 1: 45 minutes)
2.5.5. Five follow-up sessions (Three scheduled sessions in weeks 2-6; one session in week 7-10; and one session in week 14; each 15 minutes)
2.5.6. Four telephone contacts (Two scheduled contacts in weeks 2-6 [5 minutes]; two contacts in week 7-10 [15 minutes]

Intervention Type
Drug

Phase
Phase III/IV

Primary outcome(s)
Mean % of UDS negative tests for opioid class.

Key secondary outcome(s))

1. Mean % of patients completing study period (retention)
2. Mean change in the following clinical parameters (depression, anxiety, impulsiveness, addiction severity index (ASI), work and social adjustment

Completion date
31/01/2017

Eligibility

Key inclusion criteria
1. Males and females aged 18- 64 years
2. Diagnosed with current opioid use disorder (ICD-10)
3. Current use of street heroin and/or pharmaceutical opioid
4. Able to comprehend instructions and consent to the trial participation
5. Voluntarily seeking treatment
6. Able to be discharged to stable accommodation

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
64 years

Sex
Male

Total final enrolment
141

Key exclusion criteria
1. Pregnant
2. Patients with known hypersensitivity to naloxone or buprenorphine
3. Hepatic Impairment (>3 times elevated liver function)
4. Any prior suicidal attempt and current active suicide plan
5. Involvement in current criminal justice proceedings
6. Active uncontrolled severe mental illness or evidence of organic brain disease that is judged by clinical director to compromise patient safety
7. Acute and severe respiratory illness
8. Paralytic ileus
9. Benzodiazepine use (in the past 28 days) in excess of 20 mg daily diazepam equivalent ,2

Date of first enrolment
01/09/2014

Date of final enrolment
01/09/2016

Locations

Countries of recruitment
United Arab Emirates

Study participating centre
National Rehabilitation Center
Khalifa City
Shahama Rd
Near Sheikh Zayed Bridge
Abu Dhabi
United Arab Emirates
55001

Sponsor information

Organisation
National Rehabilitation Center

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
National Rehabilitation Center- UAE

Results and Publications

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/09/2022	12/08/2022	Yes	No
Protocol article	protocol	05/03/2019	05/08/2019	Yes	No
Other publications	Association of buprenorphine elimination rate constant and opioid use	12/08/2022	12/08/2022	Yes	No