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Trial of sertraline to prevent post-traumatic brain injury depression

Submission date
20/09/2022

Recruitment status
No longer recruiting

Registration date
23/12/2022

Overall study status
Ongoing

Last Edited
29/10/2025

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
Depression is very common following a traumatic brain injury (TBI), also called a head injury. Around 50% of people with a head injury will have some form of depression over the next 10 years. This is almost 10 times more common than the general public. There are two main symptoms of depression, a constant low mood and a loss of enjoyment in everyday life. Depression can affect relationships, jobs, education, financial hardship and unhealthy lifestyles like smoking and poor diets. People with depression following a traumatic brain injury tend to die earlier than the rest of the population and they are more likely to commit suicide.
Our patient and public involvement group (PPI) recognised the symptoms of depression and also mentioned others such as irritability, confusion, being very sensitive to noises and light. They agree that trying to prevent depression occurring in the first place is very important. The idea that antidepressants given early could stop depression in the first place after a traumatic brain injury was appealing. They said they would want to be given everything for the best chance of recovery. The aim of this study is to find out if a commonly used antidepressant called sertraline is better at preventing depression than a placebo (also called a dummy or 'fake' pill). The researchers will also want to study if sertraline improves quality of life, improve other symptoms like headaches, irritability, memory loss, and reduces stress for carers.

Who can participate?
Patients aged 18 years and above with mild or moderate-severe TBI

What does the study involve?
Participants will be recruited from nine Major Trauma Centres across England and from all walks of life. Patients attending A&E with a traumatic brain injury will be given information about this study. The researchers will wait for any immediate effects of the head injury, such as memory loss, to settle. Those patients who are suitable will be invited to consent to join the study. They will be randomised, that is, they will have an equal chance of receiving sertraline or a placebo. Sertraline will be started at the lowest dose which is 50 mg and after 2 weeks increase to 100 mg. In the older patient, the dose will be increased more slowly. The researchers will then see the participants again after 6 weeks and 3, 6, 9 and 12 months. At 12 months the sertraline will

be slowly reduced and stopped. The researchers will meet the participants once more at 18 months and will also seek their consent to link the research data with their GP and hospital records to see how they are getting over the next 10 years.

What are the possible benefits and risks of participating?
The researchers have brought together a unique team of senior doctors and researchers for this study. At each hospital a psychiatrist will lead the research supported by either a neurologist or neurosurgeon, so that patients are safely managed in terms of mental health and physical health. The researchers also have patient groups working with them, such as the charity Headway. They have already given feedback on the study which helped to improve the methods. After the study finishes, the results will be shared in medical journals, on social media and with leaders of the NHS so that the prevention of depression can be included for this group of patients.
The risks to participants in this study are comprised of the risks associated with the individual study procedures, and the study drug. Peripheral blood draws typically incur mild temporary discomfort. Rare but more serious risks include ecchymosis (bruise), thrombophlebitis (inflamed vein) and infection. This is a common procedure and the researchers will be using experienced phlebotomists in clinical settings to reduce these risks. There is a small but significant risk that some patients may become depressed during the study. This is one reason why a lead psychiatrist is included at each site. There is a small chance that some patients may become very depressed with possible suicidal thoughts. If this is detected during the study the researchers will ask for consent to inform their GP. If the patient does indeed develop severe depression with active suicidality, the researchers will contact the GP immediately to activate the usual care pathway for depression and/or refer to a local crisis team or A&E depending on the clinical judgement of the senior research psychiatrist and with the consent of the patient. This will be defined by a score of 1 or more on the PHQ-9 item 9 (suicidality question) followed by a clinical assessment by the research fellow. If the clinical status on the usual care pathway is indicated and/or the patient wishes it, the patient allocation will be unblinded. This would be reported as a serious adverse incident. Participants will be monitored carefully throughout their time in the study. They will be provided with an emergency number to call if necessary.

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?
July 2022 to May 2026

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

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-000072-18

Integrated Research Application System (IRAS)
1004930

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 1004930

Study information

Scientific Title
A multi-centre randomised controlled trial of the clinical and cost-effectiveness of sertraline in preventing depression in adults following a traumatic brain injury

Acronym
STOP-D (Sertraline TO prevent Post-TBI Depression)

Study objectives
Primary objective:
To test the primary hypothesis that in patients with a traumatic brain injury sertraline 100 mg od prescribed for 12 months following presentation in accident and emergency department is more effective than placebo in reducing depressive symptoms.

Secondary objectives:
1. Test the secondary hypotheses that sertraline 100 mg od prescribed for 12 months is more effective than placebo in people with post-traumatic brain injury (TBI) over 18 months in the incident rate of major depressive disorder at 12 months, reducing depressive symptoms, the incident rate of major depressive disorder, psychiatric symptoms of anxiety disorder, cognitive impairment and post-traumatic stress disorder (PTSD), alcohol and substance use, carer burden, aggressive behaviours, improving productivity, cost-effectiveness, having improved patient and carer reported outcomes
2. Assess if sertraline is associated with a greater incidence rate of adverse events than placebo
3. Assess the proportion who give consent to contact for future studies, and consent to collect data from medical records and hospital episode statistics for 10 years from recruitment
4. Collect blood and saliva for future biomarker profiling
5. Describe the patient and carer experience of the antidepressant (acceptability and changes in their mental health and social functioning)

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/12/2022, Oxford A REC (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 2071048206; oxforda.rec@hra.nhs.uk), ref: 22/SC/0310

Study design
Double-blind randomized placebo-controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied

Depressive disorder after traumatic brain injury

Interventions
Participants will be prescribed sertraline 50 mg or placebo as an oral dose (once daily [od]) daily for 2 weeks then increased to 100 mg or placebo as od daily for the next 46 weeks, consistent with evidence on optimal dosages for efficacy and acceptability. At 48 weeks, the dose will be reduced to sertraline 50 mg or placebo as od daily for 2 weeks. At 50 weeks, the dose will be reduced to 25 mg od for 2 weeks and then stopped.

Group 1: Treatment as usual (TAU) for the TBI: routine clinical management and follow-up as per local MTC guidance for the management of TBI plus placebo for 12 months. The placebo regimen will be prescribed exactly as sertraline. TAU will consist of the local MTC pathway for TBI.

Group 2: TAU plus sertraline. The researchers have selected sertraline because it has the strongest evidence for the effectiveness of treating depression; it is well tolerated in the elderly; it has the lowest epileptogenic risk. The regimen will consist of sertraline 50 mg od for 2 weeks, then increased and maintained at 100 mg od. In older adults (aged 75 years and above), the researchers will review tolerability before increasing to 100 mg. At 48 weeks, the dose will be reduced to sertraline 50 mg or placebo as od daily for 2 weeks. At 50 weeks, the dose will be reduced to 25 mg od for 2 weeks and then stopped.

Follow-up patient safety assessments will be conducted at baseline, 2, 4 and 12 weeks after randomisation to monitor hyponatraemia (below 135 mmol/l), and capacity for those who did not have mental capacity at recruitment. A standardised checklist of AEs and the Physical Symptoms/Adverse Effects check will be conducted at each IMP dispensing.

Intervention Type
Drug

Phase
Phase III

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

Primary outcome(s)
Depressive symptoms measured by Patient Health Questionnaire-9 (PHQ-9) score collected at baseline, 6, 12 and 18 months. The primary outcome will be formally assessed at 12 months.

Key secondary outcome(s))
1. Depressive symptoms measured by Patient Health Questionnaire-9 (PHQ-9) score assessed at other trial timepoints 6 and 18 months.
2. DSM (Diagnostic and Statistical Manual)-5 major depressive disorder measured by the Structured Clinical Interview (SCID) at baseline, 6, 12 and 18 months
3. Anxiety disorder measured by Generalised Anxiety Disorder-7 (GAD-7) at baseline, 6, 12 and 18 months
4. Cognitive assessment measured by Montreal Cognitive Assessment (MoCA) at baseline, 6, 12 and 18 months
5. Post-traumatic symptoms measured by Post-Traumatic Stress Disorder Checklist (PCL-5) at baseline, 6, 12 and 18 months

6. Alcohol intake measured by Alcohol Use Disorders Identification Test (AUDIT) at baseline, 6, 12 and 18 months
7. Substance use measured by Drug Abuse Screening Test-10 (DAST-10) at baseline, 6, 12 and 18 months
8. Care burden of neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q, only measured in participants with a carer) at baseline, 6, 12 and 18 months
9. Quality of life assessed using the EQ-5D and service use (to inform the economic evaluation) assessed using the Adult Service Use Schedule at baseline, 6, 12 and 18 months
10. Blood and saliva will be collected at baseline, 6, 12 and 18 months and stored within a protocol to be established pending further funding. Biomarkers analysed as part of this trial will likely include a range of inflammatory and other markers to identify those most at risk of long-term problems after traumatic brain injury (TBI) such as neurofilament light chain protein (NFL), glial fibrillary acidic protein (GFAP), tau, amyloid and Ubiquitin C-terminal hydrolase -L1 (UCH-L1)

Completion date
31/05/2026

Eligibility

Key inclusion criteria
Participant inclusion criteria as of 29/04/2024:
1. Adults aged 18 years and above
2. UK residents
3. Possible, mild or moderate-severe TBI that occurred less than 8 weeks before time of consent defined as possible, probable and definite TBIs by the Mayo Classification System
4. No current major depressive disorder as measured by the Structured Clinical Interview (SCID)

Previous participant inclusion criteria:
1. Adults aged 18 years and above
2. UK residents
3. Mild or moderate-severe TBI that occurred less than 4 weeks before time of consent defined as probable and definite TBIs by the Mayo Classification System
4. No current major depressive disorder as measured by the Structured Clinical Interview (SCID)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment

Key exclusion criteria

Participant exclusion criteria as of 29/04/2024:
1. Concurrent antidepressant medication at the British National Formulary recommended therapeutic doses for the treatment of depression
2. Other causes of acquired brain injury such as stroke
3. Known psychotic or bipolar disorders (except for mild cognitive impairment), known dementia (except for mild), actively suicidal, other acute or chronic neurological conditions except post-traumatic epilepsy, terminal or advanced medical illness such as end-stage kidney failure, heart failure, severe hepatic impairment
4. Pregnant or planning pregnancy
5. Women of childbearing potential if they are not using acceptable effective methods of contraception as defined by the Clinical Trials Facilitation Group (CTFG) (a woman is considered of childbearing potential (WOCBP), i.e. 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. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.)
Female subjects must agree to one of the following during the duration of the study:
5.1. Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.
5.2. Consistent and correct use of 1 of the following methods of birth control: a) intrauterine device (IUD) with a failure rate of <1% per year; b) tubal sterilization; c) vasectomy in the male partner; d) hormonal methods (oral contraceptives, injectable progesterone, implants of levonorgestrel, transdermal contraceptive patch, contraceptive vaginal ring). In the case of the Essure micro-insert system, this will need to be used in association with another method of contraception; Male subjects with female partners of childbearing potential must use condoms during the trial.
6. Lactating
7. Medical causes of depression such as pituitary failure
8. Known allergy to sertraline
9. Current hyponatraemia (if participant's sodium is <135 mmol/L it will be discussed with the site PI or their treating physician to confirm it is safe for the patient to be enrolled)
10. Taking medications contraindicated with sertraline as stated in the SmPC including concomitant treatment with irreversible monoamine oxidase inhibitors and pimozide
11. Participating in another CTIMP study or participated <=30 days from consent
12. Participants will be excluded if they are not able to complete self-administered questionnaires in English. (English proficiency in comatose patients will be assessed through next of kin and to the best of the ability of the clinician with the available information. Participants who come out of a coma will be reassessed for eligibility regarding English proficiency criterion. If non-proficient in English, they will be withdrawn.)

Previous participant exclusion criteria:
1. Possible TBI according to the Mayo Classification System
2. Concurrent antidepressant medication at British National Formulary recommended

therapeutic doses for treatment of depression
3. Other causes of acquired brain injury such as stroke
4. Known psychotic or bipolar disorders, known dementia, actively suicidal, other acute or chronic neurological conditions except for post-traumatic epilepsy, terminal or advanced medical illness such as end-stage kidney failure, heart failure, severe hepatic impairment
5. Pregnant or planning pregnancy
6. Women of childbearing potential if they are not using acceptable effective methods of contraception as defined by the Clinical Trials Facilitation Group (CTFG)
7. Lactating
8. Medical causes of depression such as pituitary failure
9. Known allergy to sertraline
10. Current hyponatraemia (if the participant's sodium is <130 mmol/l it will be discussed with a local hospital endocrinologist to confirm it is safe for the patient to be enrolled)
11. Taking medications contraindicated with sertraline as stated in the SmPC including concomitant treatment with irreversible monoamine oxidase inhibitors and pimozide
12. Participating in another CTIMP study or participated ≤30 days from consent
13. Participants will be excluded if they are not able to complete self-administered questionnaires in English

Date of first enrolment
01/02/2023

Date of final enrolment
23/01/2025

Locations

Countries of recruitment
United Kingdom

England

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Kings College Hospital
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Study participating centre
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Sharoe Green Lane
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PR2 9HT

Study participating centre

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Study participating centre
The James Cook University Hospital
Marton Road
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Sponsor information

Organisation
King's College Hospital

ROR
https://ror.org/044nptt90

Organisation
King's College London Hospital NHS Foundation Trust

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 data sharing plans for the current study are unknown and will be made available at a later date. The researchers will follow the NIHR data-sharing guidance. Primary research data will be made available for future analysis with adequate consent and privacy safeguards. The data will be anonymised and potential participants will be informed that information collected about them may be shared anonymously with other researchers.

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		27/10/2025	29/10/2025	Yes	No
HRA research summary			20/09/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes