ISRCTN37448835 https://doi.org/10.1186/ISRCTN37448835

MILESTONE (Emotional Cognitive Bias Modification in Depression): a trial of psychological therapy in addition to treatment with an SSRI for depression

Submission date
21/10/2020

Registration date
12/11/2020

Last Edited
18/08/2025

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
Depression affects people in different ways and can cause a wide variety of symptoms. They range from lasting feelings of unhappiness and hopelessness, to losing interest in the things you used to enjoy and feeling very tearful. Many people with depression also have symptoms of anxiety. There can be physical symptoms too, such as feeling constantly tired, sleeping badly, having no appetite or sex drive, and various aches and pains.
Recent studies indicate that drug therapy for depression is ineffective in one-third to half of patients. Furthermore, mounting evidence suggests that antidepressant drugs (e.g., selective serotonin reuptake inhibitors, SSRIs) work best in combination with psychological therapies. There is little work, however, to determine what the minimum effective psychological intervention may be in addition to drug treatment, and a similar lack of studies examining mechanisms of action of such adjunct therapies.
Processing of emotional information is critical to social functioning but is disrupted in many psychiatric disorders, including Major Depressive Disorder (MDD). We aim to investigate whether a novel Emotional Cognitive Bias Modification (CBM) psychological therapy that improves the way we see emotion in others could improve antidepressant drug efficacy.

Who can participate?
Persons aged 18 - 55 years who have a new or first episode of depression (defined as not prescribed an antidepressant in the previous 6 months) and have recently started taking an SSRI and able to have a type of brain scan (fMRI scan).

What does the study involve?
A brief (10-15 min) telephone call with a researcher to check if the study might be suitable for the participant. We would then invite the participant to an appointment (approx. 60 mins) with a researcher to discuss the study, go through a consent form, and ask the participant to complete some questionnaires. The researcher will look at the answers and tell the participant whether the participant meets the study criteria.

Eligible participants will be randomly allocated to receive one of two study therapies: One group will be given a CBM (Cognitive bias modification) therapy that aims to change the way the participant interpret emotional expressions, and the other group will receive a modified version of the CBM therapy that does not aim to change your perception of expressions. We will ask participants to complete 5 online CBM therapy sessions and then have a type of brain scan (an fMRI scan) at CUBRIC (Cardiff University Brain Research Imaging Centre). Participants will be asked to complete tasks in the scanner, which will measure if there have been any meaningful changes in brain responses that we know are linked to depression Participants will be then asked to complete an online assessment 6 weeks later. At the end of the study, participants will be informed which group they were in.

What are the possible benefits and risks of participating?
There are several benefits to taking part. We do not know whether, and how, this kind of therapy can lead to changes in the way the brain processes information. This research will lead to a better understanding of the biological basis of depression and could help in the development of new treatments for depression in the future. Taking part in research can be interesting and rewarding, however, it is important to know that the brain scan does not form part of any medical screening, diagnosis or treatment, and so it will not benefit participants directly.

Where is the study run from?
Bristol Medical School (UK)

When is the study starting and how long is it expected to run for?
January 2020 to July 2024

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

Who is the main contact?
Professor Ian Penton-Voak
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Contact information

Type(s)
Public, Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
282861

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 47029, IRAS 282861

Study information

Scientific Title
fMRI investigation of the neural mechanisms of Emotional Cognitive Bias Modification as an adjunct therapy to SSRIs in depression.

Acronym
MILESTONE RCT

Study objectives
Recent studies indicate that pharmacotherapy for depression is ineffective in one-third to a half of patients. Furthermore, mounting evidence suggests that antidepressant drugs (e.g., selective serotonin reuptake inhibitors, SSRIs) work best in combination with psychological therapies. There is little work, however, to determine what the minimum effective psychological intervention may be in addition to drug treatment, and a similar lack of studies examining mechanisms of action of such adjunct therapies.

Processing of emotional information is critical to social functioning but is disrupted in many psychiatric disorders, including Major Depressive Disorder (MDD). We aim to investigate whether a novel Emotional Cognitive Bias Modification (CBM) psychological therapy that improves the way we see emotion in others could improve antidepressant drug efficacy. Specifically, we will deliver online CBM therapy to patients taking antidepressants, with a new episode of depression. We investigate whether this leads to changes in brain activity, assessed in an MRI scanner, that have been associated with improvements in mood in earlier work. Therapeutically, this combination of CBM and antidepressants has the potential to improve patient outcomes, and this study aims to investigate the mechanisms that may underlie this possibility.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 25/11/2020, Bloomsbury Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8196; Bloomsbury.rec@hra.nhs.uk), ref: 20/LO/1118

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
GP practice

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Depression

Interventions
This is a two parallel group randomised controlled trial (RCT) with allocation at the level of the individual. Participants will be randomised to treatment with SSRIs plus Emotional Cognitive Bias Modification (CBM) or SSRI plus Sham Cognitive Bias Modification. The research team aim to recruit 84 patients.

Patients will be identified via local GP practices using record searches and direct referrals during face-to-face in person consultations, or telephone or videocall consultations. Those who are interested will be asked to complete a brief (approximately 10-15 minutes) telephone screening questionnaire to establish whether they would be eligible for a baseline interview (approximately 60 minutes).

Suitable patients would be invited to attend a baseline appointment, arranged by the researcher. This appointment will take place face-to-face in person at the patient's home, GP surgery, University of Bristol premises, or another mutually convenient location, where it is safe to do so and will take approximately 60 minutes. Alternatively, the appointment will take place remotely, with the patient completing online questionnaires on their own smartphone, tablet or computer, and the researcher providing support via telephone or videocall. Following informed consent, the assessment will
include the completion of questionnaires to establish eligibility. Patients who meet with the researcher face-to-face in person will complete paper questionnaires. For those baseline appointments that are held remotely will complete questionnaire online using on 'Jisc Online

surveys' – an online survey tool designed for academic research (https://www.onlinesurveys.ac.uk). The data is secure and strict information security standards are followed and the data is processed in compliance with GDPR.

Eligible patients will be randomised into the study and will receive either an active CBM therapy that aims to change the way the participants interpret emotional expressions, or a Sham CBM therapy, this is a modified version of the CBM therapy that does not aim to change the participants perception of expressions. Both groups will complete 4 online therapy sessions (approximately 8-12 minutes each) in the first week.

This will be followed by 1 follow up appointment involving the final therapy session then participants will be offered an fMRI scan (approx 2 hours). Participants will visit Cardiff University Brain Research Imaging Centre (CUBRIC) for an fMRI scan. CUBRIC is part of Cardiff University's Science and Innovation Campus and based in Cardiff, Wales. Travel will be arranged by the research team for participants. The study will comply with the current local COVID-19 policy.

Upon arriving at CUBRIC participants will be briefed about the scan and given an opportunity to ask questions. They will also perform an additional MRI safety check. This will confirm that nothing regarding the patient's medical history has changed since screening and they are still eligible for the scan. They will also need to be wearing MRI-compatible clothes.

Participants will practice all 3 tasks before undergoing an MRI scan. The scan will take approx 50 minutes in total and will involve the following procedures. Resting state fMRI scan of the brain (to establish baseline functional connectivity) (5 min), face processing task (15 mins), probabilistic reversal learning task (20 mins), a full anatomical MRI scan (7 min), then n-back working memory task (5 mins).

The face processing task will involve participants being presented with blocks of faces – either happy, sad or fearful faces. Participants respond by identifying the gender of the face by using the MRI-compatible button box. This will enable us to identify the neural correlates of viewing happy, sad or fearful faces. The probabilistic task will involve participants trying to determine which of two stimuli leads to reward (points gain) or loss (points deduction). This will enable us to identify the neural correlates of responding to positive and negative feedback. Finally in the n-back working memory task participants will be presented with a series of letters at the center of the screen. Participants have to respond according to whether the currently presented letter on the screen matches or doesn’t match the letter that was presented n-items. Here, there will be two blocks: 1-back and 3-back.

Finally, 6 weeks later an online follow up questionnaire will be conducted (approx 15-20 minutes). Participants who are unable to complete online will be contacted and asked to complete the questionnaires by telephone or by videocall. Participants involvement then will be complete.

Intervention Type
Mixed

Primary outcome measure
Brain activation in the amygdala in response to happy faces in comparison to rest in the amygdala, assessed by fMRI at 2 week follow-up

Secondary outcome measures

1. Happy versus sad comparisons in the amygdala, happy versus sad and happy versus rest in the medial and dorsolateral prefrontal cortex and occipital cortex, assessed by fMRI at 2 week follow-up
2. Mood assessments, both functional (e.g. quality of life assessments) and depressive and anxious symptoms assessed by questionnaires at 2 and 6 week follow-ups:
2.1. Revised Clinical Interview Schedule (CIS-R) - a detailed psychiatric instrument that will give an ICD10 diagnosis
2.2. Patient Health Questionnaire (PHQ-9) - a brief measure of depressive symptoms
2.3. General Anxiety Disorder questionnaire (GAD-7) - a brief measure of anxiety
2.4. Quality of Life Enjoyment and Satisfaction Questionnaire (QLES) - a brief measure of life enjoyment and satisfaction.
2.5. Snaith-Hamilton Pleasure Scale (SHAPS) - a measure of anhedonia

Overall study start date
06/01/2020

Completion date
31/07/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 01/12/2022:

1. Aged 18 - 55 years
2. Have a new or first episode of depression (defined as not prescribed an antidepressant in the previous 6 months)
3. Prescribed a course of SSRI medication
4. Score >10 on the PHQ-9 assessment

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Previous inclusion criteria:

1. Aged 18 - 55 years
2. Have a new or first episode of depression (defined as not prescribed an antidepressant in the previous 6 months)
3. Prescribed a course of sertraline medication
4. Score >10 on the PHQ-9 assessment

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
Both

Target number of participants
Planned Sample Size: 84; UK Sample Size: 84

Key exclusion criteria
Current exclusion criteria as of 01/12/2022:

1. Prescribed an antidepressant in the previous 6 months
2. Had a course of high intensity psychological treatment in the last 6 months
3. Alcohol or substance dependency
4. Bipolar disorder, Schizophrenia/Psychosis
5. Dementia
6. Currently under psychiatric care (including those referred but not yet seen) for depression
7. Unable to access online CBM sessions (PC, laptop, phone)
8. Cannot complete questionnaires unaided or would require an interpreter
9. Are taking part in another trial involving a psychological/drug intervention
10. Have a contra indication for fMRI scanning/imaging:
10.1 Significant hearing impairment (aids cannot be worn in the scanner)
10.2 Significant visual impairment that is not corrected by glasses/contact lenses eg, double vision or loss of vision in one eye, severe cataracts
10.3 Metal objects in or around the body which cannot be removed (braces, pacemaker, metal fragments, hearing devices, accidents involving metal fragments)
10.4 History of established central nervous system disease or injury (eg, cerebro-vascular disease, multiple sclerosis, Parkinson's disease, traumatic brain injury)
10.5 Epilepsy, type 1 diabetes or thermoregulatory problems, including Raynaud's disease
10.6 Location sensitive tattoos to the head, neck, or genital area; (patients exceeding; tattoos covering >5% of the body; longest dimension>20cm; or multiple tattoos <20cm apart will be discussed with the radiographer).
10.7 Body Mass Index >35 kg/m²
10.8 Too physically unwell to tolerate a 30-minute fMRI scan, including musculo-skeletal disorders which make lying supine and still difficult
10.9 Claustrophobia
10.10 Pregnant or trying-to-become pregnant
10.11 We will ask participants not to take recreational drugs for 72 hours prior to each test session and not to drink alcohol for 24 hours prior to each test session

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Previous exclusion criteria:

1. Prescribed an antidepressant in the previous 6 months
2. Had a course of high intensity psychological treatment in the last 6 months
3. Alcohol or substance dependency
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6. Currently under psychiatric care (including those referred but not yet seen) for depression
7. Unable to access online CBM sessions (PC, laptop, phone)
8. Cannot complete questionnaires unaided or would require an interpreter
9. Are taking part in another trial involving a psychological/drug intervention

10. Have a contra indication for fMRI scanning/imaging:
10.1 Significant hearing impairment (aids cannot be worn in the scanner)
10.2 Significant visual impairment that is not corrected by glasses/contact lenses eg, double vision or loss of vision in one eye, severe cataracts
10.3 Metal objects in or around the body which cannot be removed (braces, pacemaker, metal fragments, hearing devices, accidents involving metal fragments)
10.4 History of established central nervous system disease or injury (eg, cerebro-vascular disease, multiple sclerosis, Parkinson's disease, traumatic brain injury)
10.5 Epilepsy, diabetes or thermoregulatory problems, including Raynaud's disease
10.6 Extensive or location-sensitive tattoos, defined as covering >5% of the body; longest dimension> 20cm; multiple tattoos <20cm apart; tattoos to the head, neck or genital area
10.7 Body Mass Index >35 kg/m²
10.8 Too physically unwell to tolerate a 30-minute fMRI scan, including musculo-skeletal disorders which make lying supine and still difficult
10.9 Claustrophobia
10.10 Pregnant or trying-to-become pregnant
10.11 We will ask participants not to take recreational drugs for 72 hours prior to each test session and not to drink alcohol for 24 hours prior to each test session

Date of first enrolment
15/09/2021

Date of final enrolment
28/02/2024

Locations

Countries of recruitment
England

United Kingdom

Wales

Study participating centre
University of Bristol
School of Experimental Psychology
12a Priory Rd
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Sponsor information

Organisation
University of Bristol

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Sponsor type
University/education

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ROR
https://ror.org/0524sp257

Funder(s)

Funder type
Government

Funder Name
Medical Research Council; Grant Codes: MR/S035648/1

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
On completion of the trial, we plan to prepare peer-reviewed papers outlining the main results, and a detailed final report which will be submitted to the funder, MRC. We aim to send a

summary of the trial results to those trial participants who have indicated they would like to receive this following publication of the study findings.

Intention to publish date
01/01/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository. All data will be backed up immediately after generation onto the University of Bristol Research Data Storage Facility (RDSF). The RDSF provides secure, long-term storage for research data. This provides nightly backup of all data, with further resilience provided by three geographically distinct storage locations. A tape library is used for backup purposes and also for long-term, offline data storage. Only authorised users can access data stored within the RDSF. The RDSF is managed by Bristol's Advanced Computing Research Centre (ACRC) which has a dedicated steering group and a rigorous data storage policy (https://www.acrc.bris.ac.uk/acrc/RDSF_policy.pdf).
The RDSF upholds and reinforces Bristol's wider Information Security Policy (http://www.bris.ac.uk/medialibrary/sites/infosec/documents/isp-01.pdf).
Data will be stored in the RDSF for at least 20 years. Data on data.bris will also be stored for a minimum of 20 years.
Personal data (e.g., mood questionnaire responses, MRI scans, behavioural data collected online) will be collected during this study. Participant level data on the RDSF will be based on unique numbers assigned to each participant. These numbers will be used to link data collected online to other data sources. No sensitive or identifiable information will be kept on the RDSF. Linkage between identifying information and data (fMRI, questionnaire, online collected) will instead be stored on the secure University of Bristol. Participant consent forms will include reference to the fact that participants can withdraw their data up to ten months post study completion (in order to allow time to amalgamate data before the data is made available online) and will include details regarding the long-term plans of how the data will be stored and shared. Participant contact details and a link to participant data will therefore be kept for ten months post study completion. This metadata will be stored separately, on the secure University of Bristol Experimental Psychology server, which is encrypted, and password protected. Importantly these data will be stored on a separate server to the participant data stored on the RDSF. After one year, these electronic files containing contact details will be destroyed and all data deposited on data.bris under a level of restriction that is considered appropriate, and will be anonymised.

IPD sharing plan summary
Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version 2.0	10/11/2023	11/06/2024	No	No
Statistical Analysis Plan	version 1.2		11/06/2024	No	No