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MiTiGate trial: Is Botox more effective than lidocaine and treatment as usual in myalgia temporomandibular disorder (TMD)?

Submission date
22/12/2023

Recruitment status
Recruiting

Registration date
22/03/2024

Overall study status
Ongoing

Last Edited
15/04/2026

Condition category
Musculoskeletal Diseases

[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
Myalgia temporomandibular disorder (M-TMD) affects the muscles that move the jaw, causing pain. It affects 1 in every 15 people, and impacts on daily activities such as talking, eating, and chewing. Currently, there is no clear evidence about the best treatment, and first-line therapy is self-management for at least 6 weeks. If M-TMD pain lasts more than 3 months, then a referral to a specialist may be needed. They will usually prescribe NICE-recommended medicines amitriptyline or gabapentin ('usual treatment'). There is no clear evidence whether these are effective or which, if either, works better. Studies in other conditions that affect the pain system or muscles in the face/head show some evidence that lidocaine or botulinum toxin (Botox) injections might be helpful for M-TMD and have fewer side effects than usual treatment. This research will compare usual treatment (amitriptyline and gabapentin) against lidocaine and Botox injections to determine the best balance between effectiveness, side effects and cost. This NIHR-funded research is important to provide evidence about the most effective treatment to reduce pain and improve the quality of life for people living with M-TMD, and which is cost-effective.

Who can participate?
Patients aged 18 years and over with M-TMD

What does the study involve?
Participants may be identified by one of the 12 hospitals, by primary care or self-referral. They must be 18 years old or older with M-TMD pain for 3 months or longer that is not controlled by self-management. Participants will be randomly split equally into one of the 3 arms – usual treatment, lidocaine injections or botox injections. Some participants in North-East England will also be invited to take part in MRI scanning to explore if there are changes in the jaw joint. There are 5 visits with a 36-week treatment period, with flexibility for some remote visits for non-injection patients. For further details please contact nuth.mitigate@nhs.net.

What are the possible benefits and risks of participating?
Participants will contribute towards understanding of which is the most effective and cost-

effective first-line intervention in persistent M-TMD.
As with any trial, there are risks to the participants from the medications used in the trial. There is a large volume of safety data available for all four medications and specific risks will be explained to the participants before taking written informed consent. Two medications, gabapentin and amitriptyline, are already used as treatment as usual for this condition and the other two treatments, lidocaine and botulinum toxin type A (Botox) are also already used to treat this condition in some cases. There are some data showing that Botox may result in bony changes in the jaw joint, but the data here are contradictory and the likely clinical significance if bony changes occur is very low. The trial looks to further investigate the bone of the jaw joint through the MRI sub-study that will take place. All participants will be made fully aware of all these risks before entering into the trial. The safety of all participants will be closely monitored through adverse event reporting.
There are also risks to the participant from drug interactions and these are addressed via the detailed inclusion and exclusion criteria, and so have been mitigated in the trial design. There is also a potential risk to a foetus or baby from these medications so participants who are pregnant, planning to be pregnant or breastfeeding are excluded from the trial. All other participants will have the contraception requirements for the trial clearly explained to them and will agree to them when signing the consent form.
The participants' psychosocial distress is also monitored before the trial and within it. There are specific measures including liaison with the participant's GP and either exclusion or withdrawal from the trial if concerns exist over a participant's safety due to their mental health.
The participants will be required to attend relevant trial visits. For those participants randomised to oral medication, they do not need to return to the trial site for visits at weeks 24 and 36, they will be able to complete these visits remotely. They will, however, need to return unused trial medication after week 36 (following any tapering off of the medication, as appropriate). Those on the injectable IMP arms will need to attend in week 24 but not at week 36 which will be virtual.
The participants will be asked to complete a number of research questionnaires which will take some time. The questionnaires are at four time points which are approx. three months apart, which will limit the burden. The questionnaires are available online and can be completed in the week before the research visit, at the convenience of the participant.
Participants will be asked to undergo a pain reporting assessment and feedback as part of the trial, which involves applying varying intensity light/moderate pain stimuli to a fingernail (up to 12 times) and asking the participants to report their perceived pain scores. The aim is to ensure a more accurate reporting of pain across the trial. This assessment could cause a small amount of discomfort to the participant and could make them feel under some pressure in reporting their scores, especially if the scores do not correspond to the pain stimulus applied. It may make them feel that their reported pain is not valid or believed. Training will be provided to all investigators to ensure that the tests are administered correctly and the participants understand the reporting of the pain outcomes, without making them feel undue pressure or embarrassment. Careful attention will be paid to the language used by the investigators and scripts will be provided to investigators to try and limit any language which will make the the participant feel uncomfortable or discredited.

Where is the study run from?
Newcastle University (UK)

When is the study starting and how long is it expected to run for?
December 2023 to August 2027

Who is funding the study?
NIHR Health Technology Assessment Programme (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific, Principal investigator

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Additional identifiers

Integrated Research Application System (IRAS)
1008152

Central Portfolio Management System (CPMS)
60713

Protocol serial number
10566

Study information

Scientific Title
Managing chronic myalgia temporomandibular disorder (M-TMD): a pragmatic phase III definitive three-arm parallel-group, co-primary outcome, individually randomised open-label controlled superiority trial comparing the clinical and cost-effectiveness and safety of Botulinum toxin type A, Lidocaine, and Amitriptyline/Gabapentin, with internal pilot and cost-effectiveness analysis (MiTiGate)

Acronym
MiTiGate

Study objectives
The trial will seek to determine whether Botox or lidocaine are superior to treatment as usual (amitriptyline/gabapentin) in reducing pain intensity and improving quality of life after 36 weeks of treatment comprising 3 injection cycles. It will also assess the cost-effectiveness of all the treatments in terms of incremental cost per Quality of Life Year (QALY) gained when comparing the most effective treatment to the other treatments at 36 weeks.

The trial will have a number of secondary objectives. It will assess the cost-effectiveness of all of the treatments in terms of incremental cost per QALY over a lifetime horizon, as well as using a questionnaire (EQ-5D-5L) to evaluate whether the interventions affect generic quality of life.

The trial will examine responder rates and adherence of the participants to all of the treatments and evaluate whether any of the treatments affect jaw function. It will also evaluate whether any of the treatments affect psychosocial distress, sleep quality, or analgesia use.

It will also look at the safety of the treatments to compare the adverse effect profiles of the treatments to see if there is any difference between the treatments and to look at a small sub-group of participants who undergo an MRI to see if the treatments result in any changes in the temporomandibular joint itself.

Qualitative interviews will be used to explore treatment experiences and the acceptability of the interventions.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 06/03/2024, North East - Tyne & Wear South Research Ethics Committee (HSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 104 8282, +44 (0)207 104 8286; tyneandwearsouth.rec@hra.nhs.uk), ref: 24/NE/0019

Study design
Pragmatic Phase III definitive three-arm parallel-group co-primary outcome individually randomized open-label controlled superiority trial

Primary study design
Interventional

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Myalgia temporomandibular disorder (M TMD)

Interventions
Participants will be randomized and allocated to one of three arms:
1. Treatment as Usual (TAU): oral amitriptyline or oral gabapentin for 36 weeks
2. Lidocaine injections: three sets of injections, each 12 weeks apart
3. Botox injections: three sets of injections, each 12 weeks apart

Amitriptyline and gabapentin dosing titration and regimen are determined by clinician's usual practice but should lie within or below/slower than NICE's stated parameters (NICE, 2021):
1. Starting doses: 10 mg amitriptyline once daily in the evening; either 100mg or 300mg of gabapentin once daily, then twice daily on day 2, and then three times daily on day 3.
2. Titration interval: the quickest allowed for gabapentin and amitriptyline is 1 week and the slowest is 4 weeks.
3. Titration increments: 10 mg increments of amitriptyline. 100-300 mg increments for gabapentin which could be applied to all the three times daily regimen or one- or two of the three-times daily intakes.
4. Ceiling doses: 75 mg amitriptyline, 3600 mg gabapentin
5. Duration of therapy: trial amitriptyline or gabapentin for at least 8-12 weeks with a minimum of 2 weeks at the most effective or tolerable dose
6. Issues of tolerability will be discussed with the patient and recorded in the CRF with a possible step back to the previous dose to see if a longer duration at this dose is either more effective or allows upward titration due to the accommodation of any adverse effects.
7. Discontinuation: unless an emergency the quickest allowed discontinuation would be spread over 4 weeks or slower for amitriptyline and gabapentin in similar increments or smaller than upwards titration dose steps. Much slower tapering off over a number of months of either drug is permissible and often required/desirable.

100 units of Botox should be reconstituted with 2 ml of 0.9% normal saline once the participant attends and confirms is going ahead with treatment. Dosages per injection site are then:
1. Masseter 10 units (0.2 ml) per injection site = total 30 units per muscle
2. Temporalis 5 units (0.1 ml) per injection site = total 15 units per muscle

2 ml of 2% lidocaine will be used in the same sites and volumes as for Botox. Volumes of lidocaine per injection site are then:
1. Masseter 0.2 ml (4 mg) per injection site = total 0.6 ml per muscle
2. Temporalis 0.1 ml (2 mg) per injection site = total 0.3 ml per muscle

The cycles of injections provided will follow the schedule of events: day 0; week 12 +/- 7 days; week 24 +/- 7 days.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Botulinum toxin type A, lidocaine hydrochloride, amitriptyline hydrochloride, gabapentin

Primary outcome(s)
The trial's two co-primary outcomes for effectiveness are:
1. Characteristic pain intensity (CPI) assessed by a composite average, worst and current numerical rating scale of pain (0-100 scale) at 36 weeks of treatment examining the last 12 weeks' pain intensity
2. Disorder-specific related quality of life measured using the Oral Health Impact Profile for TMDs (OHIP-TMD) at 36 weeks of treatment examining the last 4 weeks' quality of life

The trial's primary economic outcome is:
1. Incremental cost per quality-adjusted life year gained of the most effective treatment compared to other treatments at 36 weeks, calculated using data from the use of services and productivity questionnaire (USPQ administered baseline, 12 & 36 weeks), the time and travel questionnaire (T&TQ administered at census date of 24 weeks), the EQ-5D-5L (administered at baseline, 12, 24 & 36 weeks), and routine sources and study specific estimates for unit costs

Key secondary outcome(s))
Measured between screening/baseline visit and 36 weeks:
1. Costs of care measured using the patient use of services and productivity questionnaire (USPQ) alongside the time and travel questionnaire (T&TQ)
2. Generic quality of life/utility measured using EQ-5D-5L
3. Jaw function measured using jaw function limitation questionnaire short-form
4. Psychosocial distress measured using the Patient Health Questionnaire-4 (PHQ-4)
5. Sleep quality measured using the Brief Pittsburgh Sleep Quality Index
6. Over-the-counter (OTC) analgesia measured using a daily diary
7. Structural changes and apparent diffusion coefficient (representing bone density) in the temporomandibular joint on MRI and serum biomarkers of bone turnover CTX and P1NP
8. Global impression of change in pain intensity, daily activities, emotional status, and overall status measured using a single global impression of change scale for each
9. Adverse effects measured using the Liverpool adverse effects profile
10. Longitudinal sequential qualitative data collection from a purposive sub-sample of participants using semi-structured interviews
11. A longer-term economic model will also be explored extrapolating costs and outcomes over a lifetime horizon

Completion date
31/08/2027

Eligibility

Key inclusion criteria
1. Adults ≥18 years old
2. Willing and able to give informed consent before trial procedures occurring
3. DC/TMD derived diagnosis of M-TMD with pain for ≥3 months identified as the primary complaint of familiar pain
4. Self-management trialled for ≥6 weeks and not controlled the pain to the patient's satisfaction
5. Minimum pain intensity of 30 on CPI over the last 3 months
6. For people of childbearing potential: an agreement to use at least an acceptable effective method of contraception or to practise sexual abstinence to avoid pregnancy for the duration of trial involvement.

Participant type(s)

Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Total final enrolment
0

Key exclusion criteria
A documented diagnosis or the patient reports any, of the following:
1. Current use of any of the trial interventions or has used any within the last 12 weeks*. Patients can continue any other treatment modality they currently find helpful for their TMD subject to no absolute contraindications to its use alongside the interventions under investigation.
2. Any other subtype of TMD that is the primary cause of familiar pain detected on clinical examination; familiar pain is pain provoked by clinical exam or testing/movement of a structure that matches the patient's primary complaint e.g., for M-TMD familiar pain is provoked from examination or use of the muscles of mastication. Patients can have other forms of (painful) TMD comorbid with M-TMD, but these should not be the primary cause of familiar pain determined by DC/TMD-derived diagnostic procedures.
3. Enrolled in another interventional research trial which could affect the outcome of this trial.
4. People who are pregnant, planning pregnancy, or breastfeeding during the time of the study participation*.
5. Current or planned acupuncture within the trial period or 3 months before the trial period*.
6. Lactose intolerance or lactose allergy
7. Fibromyalgia
8. Neuropathic pain
9. Coagulopathy
10. Uncontrolled hyperthyroidism
11. Renal failure
12. Severe liver disease
13. Connective tissue disorders e.g. Ehlers-Danlos syndrome, Epidermolysis bullosa, Marfan syndrome, Osteogenesis imperfecta, Rheumatoid arthritis, Poly/dermatomyositis, Scleroderma, Sjogren's syndrome, Systemic lupus erythematosus, Vasculitis
14. Any (previous) substance use disorder
15. Concerns from the research or clinical team over patient safety due to psychosocial distress, previous or current mental health illness*
16. Taking any of the following groups of medications:
16.1. Aminoglycoside antibiotics

16.2. Anticholinesterases
16.3. Non-depolarising and depolarising muscle relaxants
16.4. Opiates
16.5. Monoamine oxidase inhibitors (MAOIs)
17. Allergy or intolerance to any trial intervention
18. For the MRI sub-study group:
18.1. Cardiac pacemaker, defibrillator or pacing wires.
18.2. Cochlear implant, an aneurysm clip or a hydrocephalus shunt.
18.3. ustained injuries involving metal fragments to the eye.
18.4. Pregnancy.
18.5. Any other non-MRI-compatible implant or device.
For participants who would receive amitriptyline as treatment as usual, were they to be randomised to this arm, the following exclusions (19-24) also apply, and they would therefore be offered gabapentin instead:
19. Significant cardiovascular history as indicated by recent (less than 12 calendar months) myocardial infarction, any cardiac rhythm disorder, degree of heart block, prolonged QT interval, or coronary artery insufficiency.
20. Ileus
21. Urinary retention
22. Glaucoma
23. Orthostatic hypotension
24. Taking any of the following groups of medications:
24.1. Selective serotonin and or norepinephrine uptake inhibitors
24.2. Triptans
*If the chronology of events allows, the potentially eligible patient can be booked to be rescreened for a place on the trial at an appropriate point in the future.

Date of first enrolment
04/09/2024

Date of final enrolment
31/10/2026

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Newcastle University
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Study participating centre
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from NCTU.DataSharing@newcastle.ac.uk. Data will be made available once the trial data analysis is completed and will be available for the archive period for the trial. Each request will be reviewed by the trial team and NCTU data management team. The fully anonymised trial database can be made available. The trial PIS explains this data sharing and participants are asked to give consent for this as part of the consent process.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 1.0	20/12/2023	10/01/2024	No	No
Protocol file	version 2.0	04/03/2024	16/04/2024	No	No
Protocol file	version 4.0	17/02/2025	17/04/2025	No	No
Protocol file	version 5.0	07/10/2025	02/12/2025	No	No
Protocol file	version 6.0	05/03/2026	15/04/2026	No	No
Study website		11/11/2025	11/11/2025	No	Yes