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Amitriptyline at low-dose and titrated for irritable bowel syndrome as second-line treatment

Submission date
28/05/2019

Recruitment status
No longer recruiting

Registration date
07/06/2019

Overall study status
Completed

Last Edited
17/07/2025

Condition category
Digestive System

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

Plain English summary of protocol

Background and study aims
About 1 in 10 people report ongoing tummy pain or bloating and changes in bowel habit. These are typical symptoms of irritable bowel syndrome (IBS). IBS is a long-term condition. It causes discomfort and distress, reducing people's quality of life. There is no cure and it can be difficult to treat. IBS is also expensive, because people often visit their GP, take time off work, or need to see specialists. Small studies have shown that low dose tricyclic antidepressants (TCAs), such as amitriptyline, may be effective in treating IBS. Amitriptyline may help with IBS because it relieves pain and changes bowel activity, rather than because it affects mood. NICE guidelines suggest trying TCAs, such as amitriptyline, as second-line treatment for IBS if laxatives, loperamide, or antispasmodics have not helped. At present, given the limited evidence, there is uncertainty as to whether TCAs are effective for the treatment of IBS in primary care. The aim of this study is to find out whether a tablet called amitriptyline helps people with irritable bowel syndrome (IBS) when prescribed by GPs after other treatments such as laxatives and loperamide have not worked. The researchers are interested in its effect on both the symptoms of IBS, quality of life for people with IBS, and whether use of amitriptyline in people with IBS is likely to offer value for money to the NHS.

Who can participate?
Adults aged 18 and older with IBS that is currently symptomatic, despite having tried other treatments, and who are not currently receiving treatment at a hospital for their IBS.

What does the study involve?
Participants are randomly allocated to be given either amitriptyline or dummy (placebo) tablets. They are not aware which treatment they get. They are asked to take the tablets for 6 months. After 6 months participants are able to continue the treatment for an additional 6 months if they wish. At 12 weeks, 6 months and 12 months participants fill out questionnaires about their IBS symptoms, mood, quality of life and side effects to the medication. The researchers look at how many prescriptions for other drugs have been given to people, and how many tests or referrals have been asked for by their GP. Participants and GPs are also interviewed about their experience of being in the trial.

What are the possible benefits and risks of participating?
Patients may have improvements in their IBS symptoms, and the new knowledge gained may help others with IBS. If the study shows amitriptyline to be effective it could become widely available from the patient's GP in the near future, and help many patients other patients. Taking part in this study will also give the patients the opportunity to receive extra health checks, via the blood tests, and to discuss their IBS symptoms with healthcare professionals. Amitriptyline has been widely used for the treatment of depression since the 1960s. Common side effects include dizziness, dry mouth, constipation, and weight gain. Side effects are more common with higher dosages than are used in this trial. Patients with contraindications to amitriptyline will be declined entry into the trial. A small proportion of participants may have mild to moderate co-morbid symptoms of depression, therefore due to the unlikely, but possible, risk of amitriptyline overdose, careful monitoring of suicidal ideation will be carried out before starting, and during treatment with the study medication.

Where is the study run from?
University of Leeds (UK)

When is the study starting and how long is it expected to run for?
September 2018 to October 2022

Who is funding the study?
NIHR Health Technology Assessment (HTA) Programme (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)
2019-000324-17

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
41822; HTA 16/162/01

Study information

Scientific Title
Amitriptyline at low-dose and titrated for irritable bowel syndrome as second-line treatment (the ATLANTIS study): a double-blind placebo-controlled trial

Acronym
ATLANTIS

Study objectives
Irritable bowel syndrome (IBS) is a common, chronic, functional gastrointestinal (GI) disorder, and represents a significant financial burden to the health service. Current first-line treatment of IBS in primary care includes dietary and lifestyle advice, soluble fibre, and antispasmodic drugs. However, if these treatments are ineffective, GPs are often left with few treatment options, meaning people are frequently referred to see a specialist in secondary care, where they may be prescribed tricyclic antidepressants (TCAs) such as amitriptyline. NICE guidelines state that GPs should consider TCAs as second-line treatment for IBS if laxatives, loperamide, or antispasmodics have not helped. However, there is limited evidence to support this statement and as a result there is uncertainty as to whether TCAs are effective for the treatment of IBS in primary care. The overall aim of this study is to determine the clinical and cost-effectiveness of low-dose amitriptyline as a second-line treatment for IBS in primary care.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 02/08/2019, Yorkshire & The Humber – Sheffield Research Ethics Committee (Tudor Building, Fulwood House, Old Fulwood Road, Sheffield, S10 3TH; nrescommittee.yorkandhumber-sheffield@nhs.net; 0207 104 8084), ref: 19/YH/0150

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Irritable bowel syndrome

Interventions

The overall aim of this study is to determine the clinical and cost-effectiveness of amitriptyline as a second-line treatment for IBS in primary care. The study aims to recruit 518 adult patients with IBS in primary care, who are still symptomatic despite first-line therapies. An equal number of patients will receive amitriptyline or an identical-appearing placebo.

GP practices will identify potentially suitable patients and an invitation letter will be posted out to the patient.

SCREENING:
Potential participants will have to return a reply slip to, or email, the local recruitment hub to express their interest in the study. A research nurse will contact the patient and ask for their consent to be screened for the study. If the patient consents a screening interview will be conducted over the phone. The screening interview will take approximately 30 minutes.

BLOOD TEST APPOINTMENT/BASELINE ASSESSMENT:
If a blood test has been performed as part of local care, the results are normal, and it is within the required time-frame, it does not have to be repeated but cannot be used for trial purposes until the patient has given verbal consent. If a blood test was not performed as part of local care then the participant will be asked to provide a blood sample at their GP surgery. Women of childbearing potential, who cannot definitely confirm they are not pregnant, will be provided with a pregnancy test to do at home prior to study entry. The participant will complete either an online or a paper questionnaire at baseline.

TAKING THE DRUG:
Participants will start with taking 10 mg (1 tablet once a day at night) for 1 week. After the first week they will have the opportunity to discuss a dose change with the research nurse and then can decide whether they would like to stay on the 10 mg dose or increase their dose to 20 mg (2 tablets once a day at night). A final increase to 30 mg (3 tablets once a day at night) can be made during the third week. After this time participants can decrease or increase their dose (to a maximum of 30 mg once a day) in response to their IBS symptoms and any side effects they experience, which reflects how the treatment is used in usual clinical practice. At 6 months the participants can choose whether or not they would like to continue with the study medication for a further 6 months.

PARTICIPANT QUESTIONNAIRES:
Participants will complete online or paper questionnaires at 3 months, 6 months and at 12 months. Participants will complete the questionnaires at 12 months regardless of whether they received 6 or 12 months of treatment.

FOLLOW UP TELEPHONE CALL:
All participants will have a phone call with the research nurse at 1 week, 3 weeks, 3 months and 6 months post randomisation. Patients that continue treatment beyond 6 months will also have phone calls with the research nurse at 9 and 12 months post randomisation. The research nurse can give advice about the participant's study medication, and check if there are any problems, as well as answer any questions they may have. They will also collect data including adherence and acceptability.

WEEKLY ASSESSMENT OF IBS symptoms:
Once a week participants will be asked if the study drug is helping their IBS symptoms. The researchers will stop collecting this information for all participants at 6 months. The question will be completed online or via a paper questionnaire.

MONTH 1 OPTIONAL GP APPOINTMENT:
If the research nurse or patient has any queries about the medication or concerns the participant will have a telephone or face-to-face appointment with their GP.

END OF TREATMENT:
The participant will return any unused study medication by post. A final toxicity assessment will take place.

Intervention Type
Other

Phase
Phase III

Primary outcome(s)
Global symptoms of IBS measured using the IBS Severity Scoring System (IBS-SSS) at 6 months

Key secondary outcome(s))
1. Relief of IBS symptoms measured using the Subjective Global Assessment (SGA) of relief of IBS symptoms at 3, 6 and 12 months
2. Relief of IBS symptoms measured via a binary response to the question: “Have you had adequate relief of your IBS symptoms?” asked electronically, or via a paper-based diary, weekly until 6 months.
3. Anxiety measured using the Hospital Anxiety and Depression Scale (HADS – anxiety score) at 3, 6 and 12 months
4. Depression measured using the Hospital Anxiety and Depression Scale (HADS – depression score) at 3, 6 and 12 months
5. Healthcare use, use of other medications for IBS, and need for referral to secondary care, self-reported by the participant via a resource use questionnaire using a 3-month recall period (6-month recall period at 12 months). This will collect data concerning all resource use and medications in the community, and in primary and secondary care. Private costs and days off work related to IBS will also be collected. This will be assessed at 3, 6 and 12 months.
6. Quality-adjusted life years measured using the EQ-5D-3L at 3, 6 and 12 months
7. Ability to work and participate in other activities measured using the Work and Social Adjustment Scale (WSAS) total score at 3, 6 and 12 months
8. IBS-associated somatic symptoms measured using Patient Health Questionnaire 12 (PHQ-12) at 6 months
9. Cost-effectiveness expressed in terms of incremental cost per Quality Adjusted Life Year (QALY) at 6 and 12 months
10. Tolerability measured using the Antidepressant Side-Effect Checklist (ASEC) at 3, 6 and 12 months
11. Acceptability of treatment measured by participant self-report, as well as the decision to continue trial medication beyond 6 months. Participants will be asked “On balance do you find this medication acceptable to take and would you want to keep taking it”. This will be assessed at 6 months.
12. Adherence to therapy measured by asking the participants “Since you were last asked, which

of the options best describes how often you have taken at least one tablet of the trial medication daily?" at 3 weeks, 3, 6, 9 and 12 months
A. Every day or nearly every day
B. Half of the days or more than half of the days
C. Less than half of the days
D. None or nearly none of the days
13. Patient' and GPs' experiences of treatments and participating in the trial measured from analysis of qualitative interviews with patients and GPs at the end of the trial

Completion date
11/11/2022

Eligibility

Key inclusion criteria
1. A diagnosis of IBS (of any subtype of stool pattern [diarrhoea, constipation, mixed]) in their primary care record, and fulfilling the Rome IV criteria
2. Age > = 18 years
3. Ongoing symptoms, defined as an IBS severity scoring system (IBS-SSS) score of > = 75 at screening, despite having tried dietary changes and first-line therapies as defined by NICE (antispasmodics [e.g. mebeverine], fibre supplements [e.g. fybogel], or anti-diarrhoeals [e.g. loperamide]), assessed at screening via patient self-report
4. A normal haemoglobin, total white cell count (WCC), and platelets within the last 6 months prior to screening
5. A normal CRP within the last 6 months prior to screening
6. Exclusion of coeliac disease, via anti-tTG antibodies, as per NICE guidance
7. No evidence of active suicidal ideation, as determined by three clinical screening questions below, and no recent history of self-harm (an episode of self-harm within the last 12 months prior to screening):
7.1. Whether the patient has experienced any thoughts of harming themselves, or ending their life in the last 7-10 days?
7.2. Whether the patient currently has any thoughts of harming themselves or ending their life?
7.3. Whether the patient has any active plans or ideas about harming themselves, or taking their life, in the near future?
8. If female, must be:
8.1. Postmenopausal (no menses for 12 months without an alternative medical cause), or
8.2. Surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy), or
8.3. Using highly effective contraception (must agree to be continued for 7 days after the last dose of the investigational medicinal product)
9. Able to complete questionnaires and trial assessments
10. Able to provide written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
463

Key exclusion criteria
1. Aged > 60 years and with no GP review in the 12 months prior to screening
2. Meeting locally adapted NICE 2-week referral criteria for suspected lower gastrointestinal cancer
3. A known documented diagnosis of inflammatory bowel disease or coeliac disease
4. A previous diagnosis of colorectal cancer
5. Patients currently participating in or who have been involved in any other CTIMP trial in the previous 3 months prior to screening
6. Pregnant or breastfeeding
7. Planning to become pregnant within the next 18 months
8. Current use of a TCA, or use of a TCA within the last 2 weeks prior to randomisation, for another indication
9. Allergy to TCAs
10. Other contraindications to the use of TCAs, including patients with any of the following:
10.1. Taking monoamine oxidase inhibitors (MAOIs), or receiving them within the last 2 weeks
10.2. Already prescribed a TCA for the treatment of depression
10.3. Previous myocardial infarction
10.4. Recorded arrhythmias, particularly heart block of any degree, prolonged Q-T interval on ECG
10.5. Mania
10.6. Severe liver disease
10.7. Porphyria
10.8. Congestive heart failure
10.9. Coronary artery insufficiency
10.10. Receiving concomitant drugs that prolong the QT interval (e.g. amiodarone, terfenadine, or sotalol)
Other cautions to the use of TCAs will not be an exclusion, but these will be recorded at screening and clarified with the patient's GP and the lead GP in each hub prior to study entry.

Date of first enrolment
14/11/2019

Date of final enrolment
11/04/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
NIHR CRN: Yorkshire and Humber
-
United Kingdom
S10 2SB

Study participating centre
NIHR CRN: West of England
United Kingdom
BS1 2NT

Study participating centre
NIHR CRN: Wessex
United Kingdom
SO30 2UN

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

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
Current individual participant data (IPD) sharing statement as of 01/09/2022:
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.
CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.
The CTRU encourages a collaborative approach to data sharing, and believe it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.
The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree suitable requirements for release.

Previous individual participant data (IPD) sharing statement:
Individual participant data (with any relevant supporting material, e.g. data dictionary, protocol, statistical analysis plan) for all trial participants (excluding any trial-specific participant opt-outs) will be made available for secondary research purposes at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Requests to access trial data should be made to CTRU-DataAccess@leeds.ac.uk in the first instance. Requests will be reviewed by relevant stakeholders. No data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention requirements, which will usually stipulate that data recipients must delete their copy of the data at the end of the planned project.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		16/10/2023	20/10/2023	Yes	No
Results article	Qualitative study of patients' and GPs' views and experiences - secondary outcome	27/08/2024	29/08/2024	Yes	No
Results article		01/10/2024	15/10/2024	Yes	No
Results article		01/10/2024	17/07/2025	Yes	No
Protocol article		08/07/2022	11/07/2022	Yes	No
HRA research summary			28/06/2023	No	No
Other files	Amitriptyline for IBS dose titration document and Rationale for using Amitriptyline document	17/10/2023	26/10/2023	No	Yes
Other files	GP summary of results version 1.0	17/10/2023	26/10/2023	No	No
Other publications	Post hoc analyses	25/01/2025	28/01/2025	Yes	No
Plain English results	Lay Summary of Results version 1.0	17/10/2023	25/10/2023	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes