

Amitriptyline at Low-Dose and Titrated for Irritable Bowel Syndrome as Second-Line Treatment in primary care (ATLANTIS): a randomised, double-blind, placebo-controlled, phase 3 trial



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Summary

Background Most patients with irritable bowel syndrome (IBS) are managed in primary care. When first-line therapies for IBS are ineffective, the UK National Institute for Health and Care Excellence guideline suggests considering low-dose tricyclic antidepressants as second-line treatment, but their effectiveness in primary care is unknown, and they are infrequently prescribed in this setting.

Methods This randomised, double-blind, placebo-controlled trial (Amitriptyline at Low-Dose and Titrated for Irritable Bowel Syndrome as Second-Line Treatment [ATLANTIS]) was conducted at 55 general practices in England. Eligible participants were aged 18 years or older, with Rome IV IBS of any subtype, and ongoing symptoms (IBS Severity Scoring System [IBS-SSS] score ≥ 75 points) despite dietary changes and first-line therapies, a normal full blood count and C-reactive protein, negative coeliac serology, and no evidence of suicidal ideation. Participants were randomly assigned (1:1) to low-dose oral amitriptyline (10 mg once daily) or placebo for 6 months, with dose titration over 3 weeks (up to 30 mg once daily), according to symptoms and tolerability. Participants, their general practitioners, investigators, and the analysis team were all masked to allocation throughout the trial. The primary outcome was the IBS-SSS score at 6 months. Effectiveness analyses were according to intention-to-treat; safety analyses were on all participants who took at least one dose of the trial medication. This trial is registered with the ISRCTN Registry (ISRCTN48075063) and is closed to new participants.

Findings Between Oct 18, 2019, and April 11, 2022, 463 participants (mean age 48·5 years [SD 16·1], 315 [68%] female to 148 [32%] male) were randomly allocated to receive low-dose amitriptyline (232) or placebo (231). Intention-to-treat analysis of the primary outcome showed a significant difference in favour of low-dose amitriptyline in IBS-SSS score between groups at 6 months ($-27\cdot0$, 95% CI $-46\cdot9$ to $-7\cdot10$; $p=0\cdot0079$). 46 (20%) participants discontinued low-dose amitriptyline (30 [13%] due to adverse events), and 59 (26%) discontinued placebo (20 [9%] due to adverse events) before 6 months. There were five serious adverse reactions (two in the amitriptyline group and three in the placebo group), and five serious adverse events unrelated to trial medication.

Interpretation To our knowledge, this is the largest trial of a tricyclic antidepressant in IBS ever conducted. Titrated low-dose amitriptyline was superior to placebo as a second-line treatment for IBS in primary care across multiple outcomes, and was safe and well tolerated. General practitioners should offer low-dose amitriptyline to patients with IBS whose symptoms do not improve with first-line therapies, with appropriate support to guide patient-led dose titration, such as the self-titration document developed for this trial.

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Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder characterised by abdominal pain in association with change in stool form or frequency.¹ The condition is chronic and fluctuating,^{2,3} with a prevalence of 5% to 10% globally.⁴ Its pathophysiology is incompletely understood,⁵ and there is no cure; treatment is therefore directed at

symptoms.⁶ IBS has a considerable effect on both the individual and society. Patients with IBS can have impairments in quality of life of a similar magnitude to individuals with other chronic gastrointestinal conditions, such as Crohn's disease,⁷ and worse quality of life than patients with other chronic non-gastrointestinal diseases, such as diabetes or heart failure.⁸ Work activity

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Research in context

Evidence before this study

Most patients with irritable bowel syndrome (IBS) are managed in primary care. When first-line treatments, such as dietary changes, fibre, laxatives, or antispasmodic or antidiarrhoeal drugs do not improve symptoms, National Institute for Health and Care Excellence (NICE) guidance for the management of IBS in primary care in the UK suggests that general practitioners should consider low-dose tricyclic antidepressants as a second-line treatment. We searched PubMed with the terms “irritable bowel syndrome”, “treatment”, and “tricyclic antidepressant” to identify articles published between Jan 1, 1980, and May 23, 2023. We did not limit the search according to dose of tricyclic antidepressant studied or use any language restrictions. We identified 168 articles reporting on this issue. Although several systematic reviews and meta-analyses report that tricyclic antidepressants are efficacious for IBS, all but one of the randomised controlled trials contributing data to these meta-analyses are small and underpowered, and none were conducted entirely in primary care. This brings into question the generalisability of their findings to patients in this setting. In addition, the NICE guideline highlights the need for a trial of low-dose tricyclic antidepressants in IBS in primary care. We aimed to assess whether titrated low-dose amitriptyline was effective as a second-line treatment for IBS in primary care in a pragmatic, randomised, double-blind, placebo-controlled trial.

Added value of this study

To our knowledge, this is the largest trial of a tricyclic antidepressant in IBS ever conducted, and the first based

entirely in primary care. During 6 months of treatment, low-dose amitriptyline, titrated from 10 mg to a maximum of 30 mg once daily, was superior to placebo for both the primary and key secondary outcomes in 463 participants. Amitriptyline was also superior to placebo across multiple other symptom-based outcomes for IBS, but had no impact on somatoform symptom-reporting, anxiety, depression, or work and social adjustment scores at 6 months. Significantly more participants found low-dose amitriptyline acceptable to take than placebo and almost three-quarters adhered to the drug during the trial, with adherence generally higher in the amitriptyline group. Adverse events were more frequent with low-dose amitriptyline, and in keeping with the known anticholinergic effects of the drug, but most were judged as mild. Withdrawals due to adverse events were slightly more frequent with low-dose amitriptyline.

Implications of all the available evidence

The results of this trial of titrated low-dose amitriptyline as a second-line treatment for IBS in primary care strongly support its use in this setting. General practitioners should offer low-dose amitriptyline to patients with IBS whose symptoms do not improve with first-line therapies, with appropriate support to guide patient-led dose titration, such as the self-titration document developed for this trial. Trials of amitriptyline as a first-line therapy for IBS in primary care would be informative.

and social functioning are impaired due to the debilitating nature of symptoms.^{9,10} The annual direct and indirect costs related to IBS are considerable, estimated at £1 billion in the UK,¹¹ ¥123 billion in China,¹² and in excess of US\$10 billion in the USA.¹³

Most patients with IBS are managed by general practitioners.¹⁴ First-line therapies in primary care in the UK, as recommended by the UK National Institute for Health and Care Excellence (NICE) guideline,¹⁵ other than clear explanation of the condition and information sharing on self-management, include dietary changes and lifestyle advice, soluble fibre, laxatives, and antispasmodic or antidiarrhoeal drugs, although their efficacy is modest.^{16,17} When these are ineffective, the NICE guideline states that general practitioners should consider low-dose tricyclic antidepressants for their analgesic effect as a second-line treatment, with consideration that any benefit is uncertain. However, one study reported that less than 10% of general practitioners prescribe tricyclic antidepressants for IBS often, and only 50% believe they are effective.¹⁸ Given that 95% of general practitioners use tricyclic antidepressants to treat insomnia,¹⁹ the results of this study suggest it is uncertainty over the drug's efficacy in

IBS, rather than concerns about side-effects, that explain this.¹⁸

Meta-analyses of randomised controlled trials (RCTs) suggest a benefit of tricyclic antidepressants,^{16,20,21} possibly via their pain-modifying properties and actions on gastrointestinal motility,^{22–26} rather than any effect on mood, given the low doses used in IBS. However, almost all trials have been conducted in specialist settings, where patients tend to have more severe symptoms and it is, therefore, unclear whether tricyclic antidepressants are effective in patients with IBS seen in primary care. Indeed, the NICE guideline highlights the need for a trial of tricyclic antidepressants in IBS in primary care.¹⁵ Amitriptyline has shown promise in two previous small trials in IBS,^{27,28} is an established, inexpensive drug, which general practitioners prescribe commonly for other conditions,¹⁹ and has a well characterised safety profile.²⁹ We conducted an RCT of amitriptyline in IBS in primary care with the aim to measure the effects on global IBS symptoms at 6 months.

Methods

Study design and participants

The ATLANTIS (Amitriptyline at Low-Dose and Titrated for Irritable Bowel Syndrome as Second-Line Treatment)

trial was a randomised, double-blind, placebo-controlled, phase 3 superiority trial of amitriptyline as second-line treatment for IBS in primary care, recruiting adults with IBS (figure 1). 63% of participants recruited provided written informed consent to 12 month study participation, consisting of an initial 6 months of trial medication with the option to continue treatment for a further 6 months. Treatment duration and follow-up was curtailed to 6 months for participants recruited later, due to protocol changes during the COVID-19 pandemic. A within-study cost-effectiveness analysis was planned, but removed after a costed extension was required to complete the trial due to delays imposed by the pandemic, to minimise additional funding and prioritise funds for participant recruitment. This is now on hold, subject to further funding. A nested qualitative study exploring participant and general practitioner experiences of treatment and trial involvement will be reported separately. Patient and public involvement representatives were involved at all stages, and provided valuable contributions to trial design, documentation, and outputs.

ATLANTIS was conducted in 55 general practices in three regions, termed hubs, in England: 13 in West Yorkshire; 20 in Wessex; and 22 in West of England. The final protocol and subsequent amendments were approved by Yorkshire and the Humber (Sheffield) Research Ethics Committee (19/YH/0150) and published in full.³⁰ The trial was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki and registered with the ISRCTN Registry (ISRCTN48075063).

Eligible participants were 18 years or older, with a primary care diagnosis of IBS of any subtype (IBS with constipation [IBS-C], diarrhoea [IBS-D], mixed bowel habits [IBS-M], or unclassified [IBS-U]), and meeting Rome IV criteria for IBS (appendix, p 9).³¹ Participants had tried first-line treatments, as recommended by NICE,¹⁵ including dietary changes and lifestyle advice, soluble fibre, antispasmodics, laxatives, or antidiarrhoeals, without success, and had active symptoms, scoring 75 or more on the IBS Severity Scoring System (IBS-SSS),³² a validated, participant-reported, five-item questionnaire used widely in IBS trials. Participants also had to fulfil all

of the following inclusion criteria: normal haemoglobin, white cell and platelet count, and C-reactive protein within 6 months of eligibility screening; negative anti-tissue transglutaminase antibodies; no evidence of suicidal ideation (given that amitriptyline can be fatal in overdose); ability to complete questionnaires, trial assessments, and provide written informed consent; and, if female and not post-menopausal or surgically sterile, willingness to use highly effective contraception. Patients meeting any of the following exclusion criteria were ineligible: age 61 years or older with no general practitioner review in the 12 months prior to screening (to assess for other gastrointestinal disease); meeting NICE fast-track referral criteria for suspected lower gastrointestinal cancer;³³ coeliac disease or inflammatory bowel disease; previous colorectal cancer; involvement in another clinical trial of an investigational medicinal product; pregnancy, breastfeeding, or planning to become pregnant; or current use of, or allergy or contraindications to, a tricyclic antidepressant.³⁰

Potentially eligible patients were identified via SnoMed clinical terms searches of primary care records and were invited to take part by letter, or opportunistically, following a general practitioner visit. Interested patients were telephone screened by research nurses, followed by a clinic appointment to provide written informed consent and blood tests, with final confirmation of eligibility by the general practitioner and hub lead clinician.

Randomisation and masking

Participants were randomly assigned in a 1:1 ratio to receive amitriptyline or a matched placebo. Allocation, via a web randomisation system at the University of Leeds Clinical Trials Research Unit, was performed using minimisation, incorporating a random element to ensure treatment groups were well balanced for IBS subtype, judged via the Bristol stool form scale,³⁴ a score of 8 or more on the depression subscale of the hospital anxiety and depression scale (HADS),³⁵ and recruitment hub. All people involved directly in trial conduct and analysis (participants, general practitioners, investigators, and the analysis team) were fully masked to treatment allocation before database lock, except for unmasked safety statisticians. Trial medication was supplied by

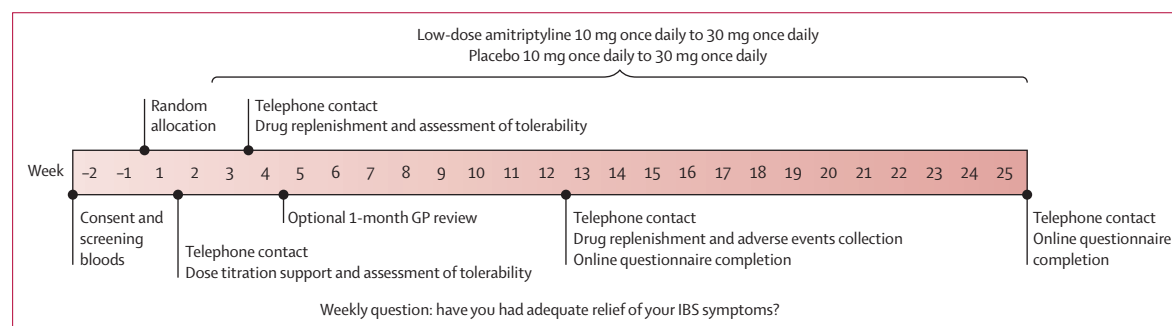
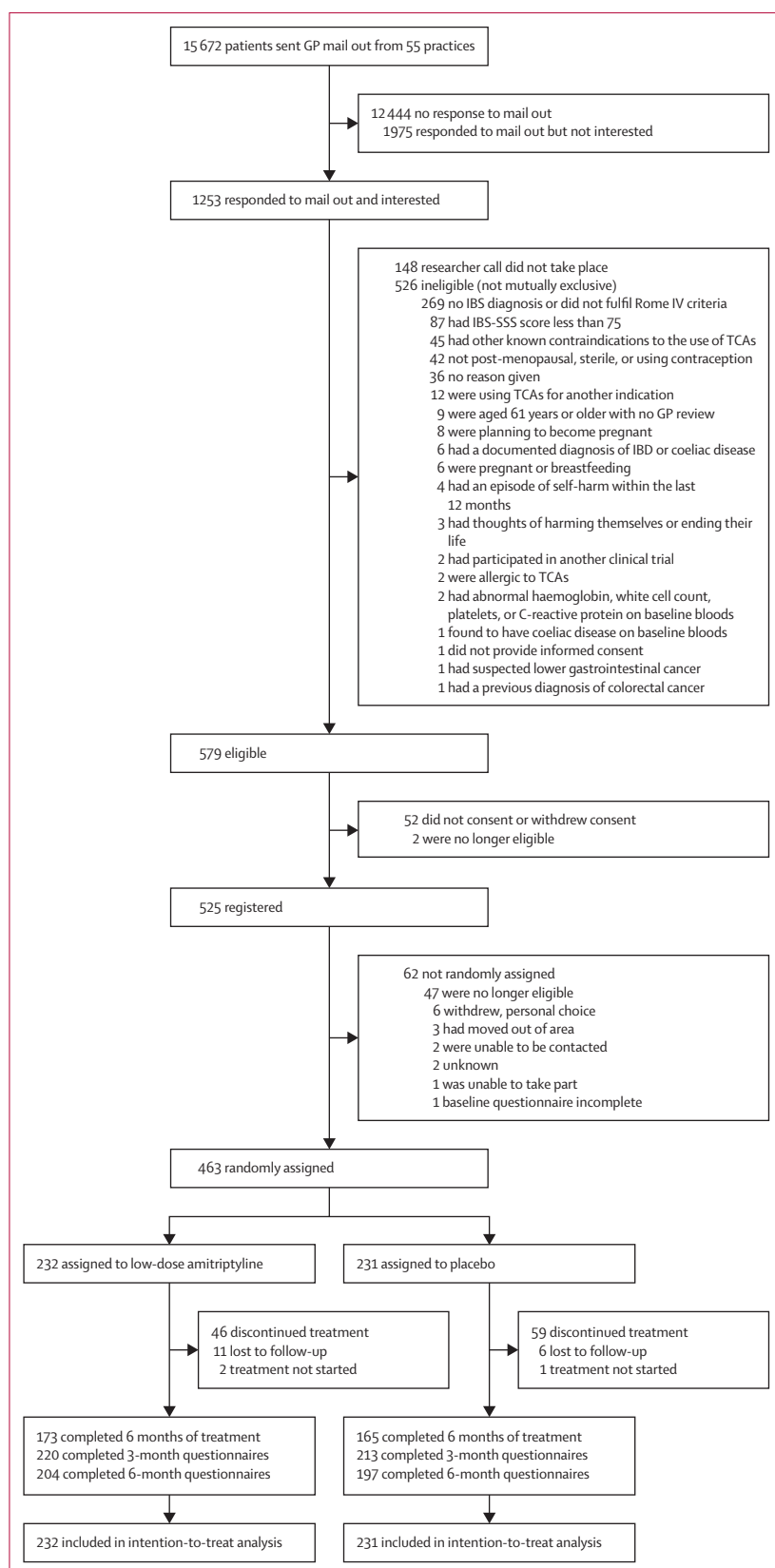


Figure 1: Flow of participants through the trial
GP=general practitioner. IBS=irritable bowel syndrome.



Modepharma (Beckenham, UK) and dispensed by post by a central pharmacy at Leeds Teaching Hospitals NHS Trust. To maintain masking, trial medication appearance, packaging, and labelling were identical in both the active treatment and placebo groups, and unique kit codes were used.

Procedures

Participants received titrated low-dose oral amitriptyline (Teva, Haarlem, Netherlands) or placebo tablets (Teva, Haarlem, Netherlands) for 6 months. All participants were provided with the NICE-approved British Dietetic Association first-line dietary advice sheet for IBS.³⁶ Usual care for IBS was provided by the participant's general practitioner, except that amitriptyline, other tricyclic antidepressants, or drugs contraindicated with tricyclic antidepressants, such as monoamine oxidase inhibitors or drugs prolonging the QT interval, were prohibited during the trial. Following random allocation, participants were offered an optional general practitioner appointment at 1 month, in case of any questions, in addition to research nurse support by telephone.

We provided standardised written information (appendix, pp 2–5), developed with input from patient and public representatives, to guide dose titration, advising participants to commence at a dose of 10 mg (one tablet) at night, with dose titration over 3 weeks, up to a maximum of 30 mg at night (three tablets), depending on side-effects and symptom response. After an initial 3 week titration, with telephone support from a research nurse at weeks 1 and 3 to assess tolerability, it was expected most participants would have reached a dosage that they would remain on for the rest of the trial. However, participants could modify dose of both the placebo and amitriptyline throughout the study in response to IBS symptoms and side-effects, reflecting amitriptyline use in usual care. Due to the risk of amitriptyline in overdose, trial medication was provided as an initial 1 month supply, followed by a 2 month and 3 month supply, with a further two 3 month supplies for those who consented to 12 month follow-up. A research nurse did a telephone review at week 3 and month 3, to ensure no development of suicidal ideation, and again at months 6 and 9 in those who consented to 12-month follow-up.

All participants completed electronic or postal questionnaires at baseline, and months 3, 6, and 12, and answered a weekly question (appendix p 6), "Have you had adequate relief of your IBS symptoms?", for the entire 6 month study duration. Text message and email

Figure 2: Study design

GP=general practitioner. IBS=irritable bowel syndrome. IBS-SSS=irritable bowel syndrome severity scoring system. TCA=tricyclic antidepressant. IBD=inflammatory bowel disease.

reminders were sent to non-responders of the questionnaires at 1 week to prompt completion, followed by a telephone call as a final reminder.

Outcomes

Full definitions of primary and secondary outcomes are provided in the appendix (pp 6–7). The primary outcome was the effect on global IBS symptoms, measured by the IBS-SSS,³² 6 months after random allocation. Questionnaire data was analysed centrally in Leeds by Clinical Trials Research Unit statisticians. A key secondary outcome was relief of IBS symptoms, measured by subjective global assessment (SGA) of relief of IBS symptoms at 6 months,³⁷ with responders defined as participants reporting their symptoms as at least somewhat relieved. Other secondary outcomes included effect on global IBS symptoms, via the IBS-SSS, and SGA of relief of IBS symptoms, at months 3 and 12, and a weekly response to the question “Have you had adequate relief of your IBS symptoms?”, with responders defined as participants reporting adequate relief for 50% of weeks or more at 6 months. We assessed IBS-associated somatic symptoms³⁸ using the Patient Health Questionnaire-12 (PHQ-12) at 6 months.³⁹ Anxiety and depression scores, via the HADS,³⁵ ability to work and participate in other activities, using the Work and Social Adjustment Scale (WSAS),⁴⁰ self-reported adherence to treatment, and tolerability of treatment, using the validated Antidepressant Side-Effect Checklist (ASEC),⁴¹ were assessed at months 3, 6, and 12, with known side-effects monitored as adverse events.

Statistical analysis

We estimated that an evaluable sample size of 414 participants provided 90% power to detect a minimum clinically important difference of 35 points between amitriptyline and placebo at 6 months on the IBS-SSS, as proposed in a previous trial of cognitive behavioural therapy in IBS,^{42,43} assuming a maximum IBS-SSS SD of 110 points,^{44,45} with 5% significance. This equates to a small to moderate effect size of 0.32. The sample size provided at least 85% power to detect a 15% absolute difference in the key secondary outcome of SGA of relief of IBS symptoms at 6 months.³⁷ We planned to recruit 518 participants, allowing for 20% loss to follow-up.³⁰

We analysed effectiveness outcomes in the intention-to-treat population, defined as all participants randomly allocated, regardless of adherence. Similarly, 12 month outcomes were analysed in the intention-to-treat population, defined as all participants who consented to to 12 month follow-up, regardless of adherence. All statistical testing used two-sided 5% significance levels, performed in SAS, version 9.4. We undertook final analysis of outcomes data once after data lock, with no interim analyses. We analysed the primary outcome using a linear regression model, adjusted for true values of minimisation variables and IBS-SSS score at baseline,

to test for differences between treatment groups on the IBS-SSS at 6 months. We imputed missing data by treatment group via multiple imputation by chained equations with 25 imputations, including recruitment hub, IBS subtype, sex, age, baseline questionnaire scores (IBS-SSS, PHQ-12, HADS, and WSAS), 3 month IBS-SSS score, and 6 month treatment status in the model. Results were calculated using Rubin’s rules for combining results of identical analyses performed on each of the imputed datasets.⁴⁶ Sensitivity analyses on the per-protocol population (defined as participants who did not majorly violate protocol, received a full 6 months’ treatment, and adhered to trial medication; appendix p 10) and on participants with complete data tested robustness of results for the primary outcome. Results were expressed as point estimates, together with 95% CIs and p values.

We analysed secondary binary outcomes (SGA of relief and acceptability) similarly, in logistic or ordinal (adherence, using the cumulative logits) regression models, expressing results as odds ratios (ORs) with 95% CIs. We analysed IBS symptoms reported weekly in a generalised linear marginal mixed repeated measures model, using available data without multiple imputation. We analysed continuous secondary outcomes at months 3, 6, and 12, including PHQ-12 (at 6 months only), HADS, and WSAS scores, as for the primary outcome, adjusted for the respective baseline score. We conducted prespecified exploratory analyses of the primary outcome, the IBS-SSS, and the key secondary outcome, SGA of relief of IBS symptoms, using alternative exploratory outcome definitions in logistic and ordinal regressions, as appropriate (appendix p 8). We conducted further prespecified (and post hoc where indicated) exploratory moderator analyses to investigate whether the 6 month treatment effect on the IBS-SSS varied by IBS subtype, HADS score, hub (post-hoc), sex (post-hoc), or baseline IBS-SSS score (post-hoc), and for the treatment effect on SGA of relief by IBS subtype and sex (both post-hoc), by including an interaction between the treatment group and each potential moderator in the primary analysis model with sensitivity analysis using complete data. We used sensitivity analyses on participants with complete data, for all secondary and exploratory outcomes, compared with analysis using multiple imputations.

We ensured that the assumptions of linear and logistic regression models were satisfied using residual plots for analysis of primary and key secondary outcomes, and a Hosmer and Lemeshow goodness of fit test and a score test for the proportional odds assumption to confirm the adequacy of the ordinal regression model.

We included all participants receiving at least one dose of trial medication, according to medication received, in the safety analysis. Descriptive statistics of self-reported adverse events on the ASEC were presented by treatment group, and the total ASEC score was analysed using

linear regression adjusted for true minimisation variables and available data for participants on treatment at months 3 and 6.⁴¹ The number of participants reporting a serious adverse event, and details of all serious adverse events, were reported for each treatment group. The number of participants withdrawing from trial treatment was reported by treatment group, with reasons. Statistical monitoring of safety data was conducted throughout the trial and reported at agreed intervals to the Data Monitoring and Ethics Committee.

Role of the funding source

The funder had no role in data collection, analysis, interpretation, writing of the manuscript, or the decision to submit for publication.

Results

Between Oct 18, 2019, and April 11, 2022, 15 672 potentially eligible patients were invited to take part and 1253 interested patients were screened (figure 2). We randomly allocated 463 (37%) of these 1253 interested patients (mean age 48.5 years [SD 16.1 years], 315 [68%] female, 148 [32%] male), to receive amitriptyline (n=232) or placebo (n=231). Participants were representative of those invited, responding, interested, eligible, and registered, in terms of age and sex (appendix p 11). Due to the COVID-19 pandemic, trial recruitment paused from March 18, to July 30, 2020, in line with national guidance, and restarted on July 31, 2020. Trial follow-up completed in October 2022, with 6 month follow-up completed for 401 (87%) participants (204 [88%] of 232 in the amitriptyline group, 197 [85%] of 231 in the placebo group; appendix p 12). Study withdrawals from optional interviews, monthly or weekly questionnaires, or from further data collection occurred in 23 (5%) of all participants. 14 (3%) participants (four [2%] in the amitriptyline group and ten [4%] in the placebo group) took the optional 1 month general practitioner appointment. All participants assigned to treatment were included in the intention-to-treat analyses. Protocol violations occurred in six (1%) participants; four were major violations and were therefore excluded from the per-protocol analysis (details of major violations can be found in the appendix; p 10).

Participant demographics and baseline characteristics are shown in table 1. Over 80% (372 of 463) of participants had IBS-D or IBS-M, 84% (390 of 463) had a normal HADS-depression score, and 85% (392 of 463) of participants had moderate to severe scores on the IBS-SSS. The mean IBS-SSS score in all participants was 272.8 (SD 90.3) and the median duration of IBS was 10 years.

In total, 338 (73%) of all participants completed 6 months' treatment; 173 (75%) in the amitriptyline group and 165 (71%) in the placebo group (appendix p 13). 105 (23%) of all participants discontinued trial medication before 6 months; 46 (20%) in the amitriptyline

group and 59 (26%) in the placebo group. The most common reason for discontinuation was adverse events, in 30 (13%) participants allocated to amitriptyline and 20 (9%) allocated to placebo, followed by perceived lack of benefit in seven participants (3%) and 18 participants (8%) respectively. A further 17 (4%) participants (11 [5%] in the amitriptyline group and six [3%] in the placebo group) were lost to follow-up, and three (1%) did not commence treatment. Of the participants completing 6 months treatment, similar proportions of participants in both groups reported making dietary modifications, changing their exercise regimen, or commencing a new drug for IBS, other than a tricyclic antidepressant, during the trial (appendix p 14). By 3 months, similar proportions of participants allocated to the amitriptyline group were taking once daily doses of either 20 mg (68 [35%] of 193) or 30 mg (73 [38%] of 193), although by 6 months this increased to 43% taking 30 mg daily. However, in the placebo group 57% of participants (106 of 186) titrated their dose to 30 mg once a day by 3 months, and this remained similar at 6 months (appendix p 15).

Amitriptyline was superior to placebo at 6 months in the intention-to-treat analysis for the primary outcome, with a significant mean difference in IBS-SSS score between groups (−27.0; 95% CI −46.9 to −7.1; $p=0.0079$, table 2), and the key secondary outcome, with increased odds of SGA of relief of IBS symptoms (OR 1.78; 95% CI 1.19 to 2.66; $p=0.0050$, table 2 and figure 3). The difference in mean change in IBS-SSS score was also significant at 3 months (−23.3; 95% CI −42.0 to −4.6; $p=0.014$), as was SGA of relief of IBS symptoms at 3 months (OR 1.70, 95% CI 1.15 to 2.53; $p=0.0080$; table 2).

Amitriptyline was also superior to placebo for adequate relief of IBS symptoms, with an increased odds of adequate relief across all weeks during the 6 months (OR 1.56, 95% CI 1.20–2.03; $p=0.0008$; table 2, appendix p 22), and an increased proportion of participants reporting relief for 50% of weeks during the 6 months (90 of 222 [41%] vs 67 of 221 [30%]). Overall, more participants found amitriptyline acceptable than placebo, and would have been willing to continue taking it at 6 months (1.60; 1.08–2.35, $p=0.018$). Self-reported adherence at 3 months was similar between treatment groups, but by 6 months more participants in the amitriptyline group compared to the placebo group (172 of 232 [74%] vs 155 of 228 [68%]) reported being adherent to trial medication. There was no evidence of an effect on PHQ-12 scores at 6 months, or on HADS-anxiety, HADS-depression, or WSAS scores at either month 3 or 6 (table 2).

In our prespecified exploratory outcomes (appendix pp 16, 23–24), there was an increased odds for IBS-SSS to reduce by at least 50 points with amitriptyline at both 3 months (OR 1.49, 95% CI 0.97–2.28; $p=0.068$) and 6 months (1.48, 0.97–2.27; $p=0.068$), but this was not significant. Significantly more participants allocated to amitriptyline experienced a 30% or greater decrease in

	Low-dose amitriptyline (n=232)	Placebo (n=231)
Mean age, SD	49.2 (16.2)	47.8 (15.9)
Sex		
Female	156 (67%)	159 (69%)
Male	76 (33%)	72 (31%)
Ethnicity		
White	226 (97%)	225 (97%)
Other*	6 (3%)	6 (3%)
IBS subtype		
IBS-C	40 (17%)	37 (16%)
IBS-D	92 (40%)	89 (39%)
IBS-M	93 (40%)	98 (42%)
IBS-U	7 (3%)	7 (3%)
Hub		
West Yorkshire	43 (19%)	44 (19%)
West of England	92 (40%)	92 (40%)
Wessex	97 (42%)	95 (41%)
IMD quintile†		
1	13/229 (6%)	13/230 (6%)
2	34/229 (15%)	27/230 (12%)
3	38/229 (17%)	33/230 (14%)
4	75/229 (33%)	74/230 (32%)
5	69/229 (30%)	83/230 (36%)
Median years from IBS diagnosis, IQR	10 (4–21)	9 (4–18)
Mean IBS-SSS‡, SD	273.4 (90.5)	272.1 (90.3)
IBS-SSS severity§		
Mild (75–174)	37 (16%)	26 (11%)
Moderate (175–299)	98 (42%)	103 (45%)
Severe (300–500)	94 (41%)	97 (42%)

(Table 1 continued in next column)

	Low-dose amitriptyline (n=232)	Placebo (n=231)
(Continued from previous column)		
Mental health		
Mean PHQ-12 score‡, SD	6.3 (3.5)	6.3 (3.6)
Mean HADS-anxiety score‡, SD	7.3 (4.3)	7.7 (4.3)
HADS-anxiety score ≥8	106 (46%)	112 (48%)
Previously treated for anxiety	80 (34%)	79 (34%)
Mean HADS-depression score‡, SD	4.4 (3.6)	4.1 (3.2)
HADS-depression score ≥8	37 (16%)	36 (16%)
Previously treated for depression	79 (34%)	99 (43%)
Mean WSAS score‡, SD	11.2 (8.2)	11.5 (7.6)
Previous first-line treatments¶	232 (100%)	231 (100%)
Previous dietary changes	232 (100%)	231 (100%)
Antispasmodics	176 (76%)	183 (79%)
Antidiarrhoeals	70 (30%)	75 (32%)
Fibre supplements	52 (22%)	52 (23%)
Laxatives	51 (22%)	34 (15%)
Peppermint oil	18 (8%)	27 (12%)

All data are n (%) unless otherwise specified. IBS=irritable bowel syndrome. IBS-C=irritable bowel syndrome with constipation. IBS-D=irritable bowel syndrome with diarrhoea. IBS-M=irritable bowel syndrome with mixed bowel habits. IBS-U=irritable bowel syndrome unclassified. IMD=index of mean deprivation. IBS-SSS=Irritable Bowel Syndrome Severity Scoring System. PHQ-12=Patient Health Questionnaire-12. HADS=Hospital Anxiety and Depression Scale. WSAS=Work and Social Adjustment Scale. *Data have been grouped into Other to preserve anonymity. †Quintiles represent the measure of relative deprivation for neighbourhoods in England. Quintile 1=bottom 20%; quintile 2=21–40%; quintile 3=41–60%; quintile 4=61–80%; quintile 5=top 20%. ‡Lower scores are better. §Eight participants with an IBS-SSS of 75 or more points at eligibility screening had a score less than 75 points at the time of random allocation, but were included as they met eligibility criteria at screening. ¶Not mutually exclusive.

Table 1: Baseline characteristics

abdominal pain severity on the IBS-SSS at 6 months (1.66, 1.12–2.46; $p=0.012$) but not in abdominal distension severity. Using an alternative definition of SGA of relief of IBS symptoms, where only those reporting considerable or complete relief at months 3 or 6 were considered responders, an increase in the effect size for amitriptyline was observed at both 3 months (1.81, 1.17–2.79; $p=0.0078$) and 6 months (1.88, 1.20–2.95; $p=0.0057$); results of ordinal regression of SGA of relief of IBS symptoms were comparable to the primary analysis. Sensitivity analyses on the per protocol population for the primary outcome, and on participants with complete data for the primary and key secondary outcomes, gave consistent results, albeit with larger estimated treatment effects. For 12 month analyses and prespecified and post-hoc exploratory moderator analyses, see the appendix (pp 1, 18–21, 27–35).

Table 3 reports treatment-emergent adverse events at months 3 and 6, as captured by the ASEC for participants

still on treatment, as known side-effects were being collected as adverse event outcomes. There was a significant increase in the total ASEC score in the amitriptyline group compared with the placebo group at 3 months (1.39, 95% CI 0.29 to 2.50; $p=0.013$), but not at 6 months (0.26, –0.98 to 1.51; $p=0.68$). Adverse events with amitriptyline related mainly to its known anticholinergic effects, including dry mouth (90 [54%] of 166 at 6 months), drowsiness (88 [53%] of 166), blurred vision (28 [17%] of 166), and urination problems (36 [22%] of 166). However, few (<5%) were severe, except for constipation and diarrhoea (<10%; appendix pp 25–26). For adverse events leading to treatment discontinuation, see appendix p 17. There were five serious adverse reactions (two in the amitriptyline group and three in the placebo group), and five serious adverse events unrelated to trial medication (four in amitriptyline, one in placebo). Owing to the small numbers, we are not reporting details to preserve the anonymity of participants.

	3 months				6 months			
	Low-dose amitriptyline (n=232)	Placebo (n=231)	Effect*, 95% CI	p value	Low-dose amitriptyline (n=232)	Placebo (n=231)	Effect*, 95% CI	p value
Primary outcome								
IBS-SSS†								
Mean total IBS-SSS‡, SD	173.0 (106.6), n=219	194.6 (107.5), n=213	-23.3 (-42.0 to -4.6)	0.014	170.4 (107.7), n=204	200.1 (114.5), n=197	-27.0 (-46.9 to -7.1)	0.0079
Change in IBS-SSS from baseline, SD	-99.8 (107.7)	-76.1 (107.1)	..	..	-99.2 (112.9)	-68.9 (109.3)	..	..
Secondary outcomes								
SGA of relief of IBS symptoms§	139/220 (63%)	105/213 (49%)	1.70 (1.15 to 2.53)	0.0080	125/204 (61%)	88/195 (45%)	1.78 (1.19 to 2.66)	0.0050
Adequate relief of IBS symptoms for 50% of weeks during the 6 months¶	NA	NA	NA	..	90/222 (41%)	67/221 (30%)	1.56 (1.20 to 2.03)	0.0008
Mean PHQ-12 score‡, SD	NA	NA	NA	..	5.7 (3.4), n=202	5.9 (3.2), n=192	-0.04 (-0.58 to 0.49)	0.88
Mean HADS-anxiety score‡, SD	6.5 (4.4), n=220	6.6 (4.0), n=212	0.05 (-0.53 to 0.63)	0.86	6.7 (4.4), n=203	6.9 (4.0), n=193	0.08 (-0.49 to 0.65)	0.78
Mean HADS-depression score‡, SD	3.5 (3.3), n=220	3.6 (3.2), n=212	-0.22 (-0.71 to 0.26)	0.37	3.9 (3.6), n=202	4.0 (3.5), n=193	-0.20 (-0.75 to 0.34)	0.46
Mean WSAS score‡, SD	9.3 (7.6), n=210	9.5 (6.3), n=198	-0.27 (-1.36 to 0.83)	0.63	8.1 (7.6), n=195	9.4 (7.8), n=184	-1.04 (-2.30 to 0.23)	0.11
Acceptability of treatment	NA	NA	NA	..	122/211 (58%)	100/213 (47%)	1.60 (1.08 to 2.35)	0.018
Adherence to treatment	193/232 (83%)	183/220 (83%)	..	..	172/232 (74%)	155/228 (68%)	..	..

IBS-SSS=Irritable Bowel Syndrome Severity Scoring System. SGA=subjective global assessment. IBS=irritable bowel syndrome. PHQ-12=Patient Health Questionnaire-12. HADS=Hospital Anxiety and Depression Scale. WSAS=Work and Social Adjustment Scale. NA=not applicable. *Effect represents the mean difference between treatment groups for continuous outcomes (IBS-SSS total score, PHQ-12, HADS, and WSAS) and odds ratios for binary outcomes (SGA of relief of IBS symptoms and acceptability) estimated using linear and logistic regression adjusted for stratification variables, and baseline score in linear regression. Missing data imputed via multiple imputation. †Lower scores are better. ‡Primary outcome at 6 months. §Key secondary outcome at 6 months. ¶In/N (%) indicates the number of participants with adequate relief for 50% of weeks during the 6 months, whereas effect indicates odds of adequate relief across all weeks during the 6 months with amitriptyline relative to placebo estimated from a generalised linear marginal mixed model of weekly data. ||Defined as being on medication every day or nearly every day, or on half the days or more than half the days; proportional odds assumption not satisfied, descriptive analysis only.

Table 2: Primary outcome at 6 months and secondary outcomes at 3 and 6 months

Discussion

To our knowledge, this is the largest trial of a tricyclic antidepressant in IBS ever undertaken and the first based entirely in a primary care setting. It addresses a key research priority identified by NICE guidance for management of IBS in primary care.¹⁵ In a population not experiencing any benefit from first-line therapies, with a long duration of disease and moderate to severe symptoms, low-dose amitriptyline met the primary outcome, with a mean decrease in IBS-SSS of almost 100 points at both months 3 and 6 compared with baseline, and also met the key secondary outcome for effectiveness, as well as other IBS symptom measures. There was no effect of low-dose amitriptyline on somatoform symptom-reporting scores, or anxiety or depression scores, during 6 month follow-up, nor was there any impact on work and social activities. More participants found low-dose amitriptyline acceptable to take compared with placebo, and almost three-quarters of participants adhered to the drug during the 6 month trial. Adverse events were more frequent with low-dose amitriptyline than with placebo. Adverse events reported by participants receiving amitriptyline in excess of those

reported by the placebo group mainly related to amitriptyline's anticholinergic effects, including drowsiness and dry mouth. However, for most participants, these effects were judged as mild, although withdrawals from the study due to adverse events were slightly more frequent with low-dose amitriptyline.

The 6 month duration of treatment in ATLANTIS is longer than most drug trials in IBS, where efficacy is usually assessed over 12 weeks. Our study is, therefore, in line with European Medicines Agency recommendations for IBS treatment trials,⁴⁷ and the results are likely to be more representative of the effectiveness of low-dose amitriptyline for a condition that, for many people, is chronic and relapsing.² We used outcomes that are widely accepted in trials conducted in IBS, including a mean change in the total IBS-SSS and adequate relief of symptoms of IBS. Effectiveness analyses were conducted on all participants, irrespective of adherence, with imputation of missing data. Therefore, it is unlikely we have overestimated the effectiveness of low-dose amitriptyline for IBS in primary care. We used current recommended symptom-based criteria, the Rome IV

criteria, together with limited diagnostic testing to exclude known organic mimics of IBS in all participants, in line with UK guidance.^{6,15} We recruited participants with IBS, irrespective of predominant stool pattern, with symptoms of varying severity, from a broad range of general practices in three different regions of the UK, meaning our results are likely to be generalisable to many patients in this setting. Follow-up rates for participant-reported outcomes at 6 months were 87%, preserving power despite the slightly smaller than projected sample size. In terms of where trials lie on the pragmatic-explanatory continuum, ATLANTIS leaned strongly towards the pragmatic end for six of the nine PRECIS-2 criteria,⁴⁸ including eligibility, setting, organisation, flexibility of delivery of the intervention, primary outcome, and primary analysis.

Our chosen primary outcomes differed from US Food and Drug Administration (FDA) and European Medicines Agency recommendations for drug trials in IBS.^{47,49} These recommendations would have been impractical in a pragmatic 6 month trial, recruiting participants in primary care with IBS of all subtypes, including IBS-M or IBS-U, for which there is no consensus on recommended endpoints. Our exploratory outcomes of a 30% or greater improvement in abdominal pain on the IBS-SSS and adequate relief of IBS symptoms in 50% of weeks, both of which were significantly higher with low-dose amitriptyline, approximate to FDA-recommended and European Medicines Agency-recommended endpoints, and are more stringent but did not require completion of a daily diary outcome specific to IBS subtype. Participants were primarily White, despite considerable efforts to reach out to people of different ethnicities with IBS during the trial. However, unlike many treatment trials in IBS more than 30% of recruited participants were male, and age and deprivation indices were wide ranging. Over 80% of participants had IBS-D or IBS-M, meaning effectiveness of low-dose amitriptyline in those with IBS-C or IBS-U might be more difficult to judge. Our participant information leaflet mentioned constipation was a potential side-effect of amitriptyline, and perhaps deterred patients with IBS-C from participating. Given the higher rates of anticholinergic side-effects in the amitriptyline group, there is the possibility that some participants guessed correctly they were receiving the active drug, and that this has influenced findings.

The use of the Rome IV criteria leads to the selection of a group of patients with higher symptom severity,⁵⁰ borne out by the mean IBS-SSS scores at baseline, which were in the moderate to severe range. The median duration of IBS among participants was 10 years. Given this, and the 6 month treatment duration, the placebo response rates seen in the trial might appear relatively high, and the 35-point minimum clinically important difference was not met, although the 95% CI included 35 points and excluded the possibility of no effectiveness of amitriptyline. The

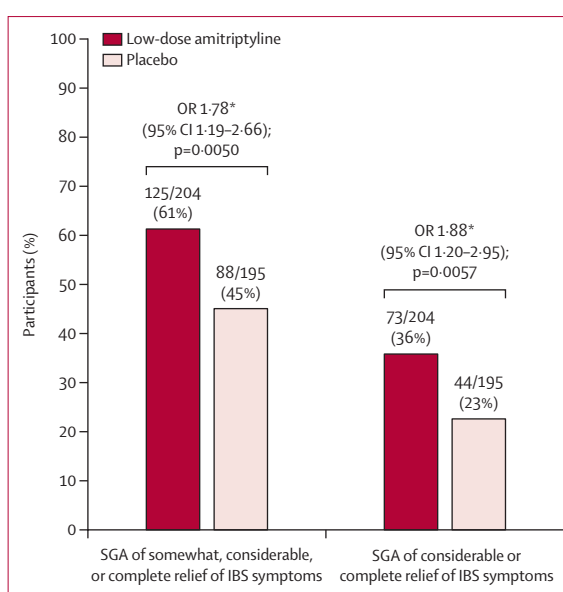


Figure 3: Key secondary outcome of SGA of relief of IBS symptoms at 6 months
SGA=subjective global assessment. IBS=irritable bowel syndrome. OR=odds ratio. HADS=Hospital Anxiety and Depression Scale. *All ORs were estimated using logistic regression adjusted for recruiting hub, IBS subtype, and HADS-depression score. Missing data were imputed via multiple imputation.

35-point minimum clinically important difference was derived from a pilot trial,⁵¹ and although it has been used as an endpoint in a trial of cognitive behavioural therapy in IBS,⁴³ this was in comparison with treatment as usual and the participants were not masked, so knew whether they received active treatment. ATLANTIS was masked and placebo-controlled, and there is evidence that patients with IBS are more likely to respond to placebo than a control intervention of no treatment.^{52,53} Other possible explanations include provision of the British Dietetic Association dietary advice sheet to all participants, regular follow-up, usual general practitioner care throughout, and telephone calls from a research nurse to assist with dose titration and trial medication reissue. However, numbers of participants reporting having made dietary changes or having commenced a new drug for IBS were relatively small, and similar between treatment groups. Participants could also have felt more in control of their symptoms and empowered through being able to self-titrate their dose in response to symptoms and side-effects. Additionally, regression towards the mean during follow-up is well recognised in clinical trials. This makes it particularly noteworthy that despite the placebo response rates observed, there was still a significant difference in effectiveness with amitriptyline over placebo.

Although previous meta-analyses of tricyclic antidepressants in IBS demonstrate these drugs, as a class, are superior to placebo,^{16,20,21} the included trials have been relatively small, with a maximum treatment duration of 3 months, and none have been conducted entirely in primary care. The largest RCT to date used 150 mg

	3 months		6 months	
	Low-dose amitriptyline (n=231)*	Placebo (n=229)*	Low-dose amitriptyline (n=232)†	Placebo (n=228)†
Number of participants on treatment	194	196	174	164
Number of participants on treatment and completing the ASEC	193	192	166	152
Total ASEC score‡				
Mean, SD	9.9 (6.0); n=193	8.4 (5.7); n=192	9.3 (6.1); n=166	8.7 (6.2); n=152
Mean difference (95% CI); p value§	1.39 (0.29 to 2.50); p=0.013	..	0.26 (-0.98 to 1.51); p=0.68	..
Side effect				
No side effects reported	5/193 (3%)	7/192 (4%)	2/166 (1%)	3/152 (2%)
≥1 mild to severe side effect	188/193 (97%)	185/192 (96%)	164/166 (99%)	149/152 (98%)
≥1 moderate to severe side effect	156/193 (81%)	154/192 (80%)	127/166 (77%)	113/152 (74%)
≥1 severe side effect	58/193 (30%)	46/192 (24%)	45/166 (27%)	37/152 (24%)
Side effects reported at any frequency				
Dry mouth	122/193 (63%)	87/192 (45%)	90/166 (54%)	56/152 (37%)
Drowsiness	128/193 (66%)	67/192 (35%)	88/166 (53%)	52/152 (34%)
Insomnia	78/193 (40%)	108/192 (56%)	77/166 (46%)	96/152 (63%)
Blurred vision	29/193 (15%)	24/192 (13%)	28/166 (17%)	14/152 (9%)
Headache	74/193 (38%)	85/192 (44%)	78/166 (47%)	80/152 (53%)
Constipation	110/193 (57%)	89/192 (46%)	93/166 (56%)	78/152 (51%)
Diarrhoea	117/193 (61%)	126/192 (66%)	98/166 (59%)	103/152 (68%)
Increased appetite	54/193 (28%)	44/192 (23%)	45/166 (27%)	34/152 (22%)
Decreased appetite	34/193 (18%)	28/192 (15%)	17/166 (10%)	22/152 (14%)
Nausea or vomiting	35/193 (18%)	26/192 (14%)	26/166 (16%)	26/152 (17%)
Problems with urination	31/193 (16%)	23/192 (12%)	36/166 (22%)	20/152 (13%)
Problems with sexual function	29/193 (15%)	23/192 (12%)	24/166 (14%)	16/152 (11%)
Palpitations	56/193 (29%)	37/192 (19%)	41/166 (25%)	38/152 (25%)
Light-headed on standing	73/193 (38%)	63/192 (33%)	69/166 (42%)	54/152 (36%)
Feeling like the room spinning	29/193 (15%)	24/192 (13%)	20/166 (12%)	19/152 (13%)
Sweating	71/193 (37%)	60/192 (31%)	54/166 (33%)	49/152 (32%)
Increased body temperature	56/193 (29%)	48/192 (25%)	35/166 (21%)	36/152 (24%)
Tremor	17/193 (9%)	13/192 (7%)	13/166 (8%)	11/152 (7%)
Disorientation	24/193 (12%)	8/192 (4%)	13/166 (8%)	10/152 (7%)
Yawning	67/193 (35%)	68/192 (35%)	63/166 (38%)	50/152 (33%)
Weight gain	72/193 (37%)	59/192 (31%)	73/166 (44%)	49/152 (32%)

Data are n/N (%) unless otherwise stated. ASEC=Antidepressant Side Effect Checklist. *Two participants allocated to amitriptyline and one allocated to placebo did not commence treatment. In addition, one participant allocated to placebo was mailed the wrong trial medication due to a kit number identification error and received amitriptyline. The participant was informed, classed as a protocol violation, and withdrawn from the trial. †Between 3 and 6 months, one participant in the placebo arm took a single 30 mg dose of their friend's amitriptyline as they were away and had forgotten their trial medication. ‡Lower scores are better. §Estimated using linear regression for participants on treatment with complete data, adjusted for stratification variables. For a breakdown of serious adverse events please see the appendix (pp 25–26).

Table 3: Overview of treatment-emergent adverse events at 3 and 6 months in the safety analysis set

desipramine once daily, recruiting a mixed population of 216 female patients with functional bowel disorders, 172 of whom had IBS.⁵⁴ Similar to our trial, the most common side-effects were related to the anticholinergic effects of the drug. More patients discontinued desipramine due to adverse events than in our trial, which could reflect the higher dosage used. Their primary outcome, a composite of patient satisfaction, symptom improvement, and increased engagement in social activities, was not met,

with a 60% response rate with desipramine versus 47% with placebo. However, subgroup analyses demonstrated desipramine was superior to placebo in those with moderate, rather than severe, symptoms, and those with IBS-D. Presence of abnormal baseline depression scores had no effect on treatment response. In another trial conducted in 54 patients with IBS-D in secondary care,²⁸ response rates with 10 mg amitriptyline once daily were 70%, compared with 41% for placebo, but this was not

statistically significant, probably due to an underpowered RCT. Adverse event rates were similar between treatment groups.

In our trial, treatment effects were generally larger in those with IBS-C or IBS-D, lower baseline HADS-anxiety scores, higher baseline IBS-SSS scores, and among men. The magnitude of the difference in treatment effect increased between months 3 and 6, and remained similar at 12 months, although this was no longer statistically significant. This underlines the importance of allowing adequate time for low-dose amitriptyline to have a beneficial effect in IBS, and is compatible with reports of a decrease in placebo response rates as trial duration increases.⁵⁵ We observed no effect of low-dose amitriptyline on somatoform symptom-reporting, anxiety, or depression scores during the 6 months of treatment. This supports a benefit of low-dose amitriptyline in IBS arising from its peripheral actions on gastrointestinal motility and pain sensation,^{26,56} rather than improvements in extra-intestinal symptoms, anxiety, or depression, which are often associated with IBS.^{38,57} Nor was there any impact on ability to work or social functioning, according to the WSAS at 6 months, although reduction in scores was generally greater in the low-dose amitriptyline group. It could be that the treatment duration was too short to see any meaningful improvement, given WSAS scores were significantly lower with amitriptyline at 12 months. HADS-depression scores were also significantly lower with amitriptyline by 12 months. However, strong conclusions cannot be drawn from month 12 outcomes, because curtailment of follow-up due to the pandemic reduced the intended sample size, and participants were no longer randomised, as they had the option to continue or cease trial medication.

In conclusion, this trial of low-dose amitriptyline, 10 mg to 30 mg once daily, as second-line therapy in 463 participants with IBS in primary care has addressed an important unanswered question. Amitriptyline was more effective than placebo across a range of IBS symptom measures, and was safe and well tolerated, when titrated according to symptom response and side-effects. When the rationale for use of a tricyclic antidepressant for IBS is explained clearly, as in the information materials provided to participants in this trial, with appropriate support, many people with IBS find it acceptable and beneficial. General practitioners should offer low-dose amitriptyline to patients with IBS in whom first-line therapies are ineffective, with appropriate support to guide patient-led dose titration, such as the self-titration document we developed. Management guidelines should be updated to reflect these findings.

Contributors

ACF co-conceived and designed the ATLANTIS trial and had overall responsibility in his role as co-chief investigator. AW-H provided statistical input into the implementation and statistical analysis plan, under the supervision of AJF. SLA contributed to the design of the trial, participant enrolment, and data acquisition. P-LO provided statistical

input into the implementation and statistical analysis plan, under the supervision of AW-H and AJF. MJR and RF contributed to the design of the trial, participant enrolment, and data acquisition. DC, AH, SN, and RT all contributed to participant enrolment and data acquisition. FLB designed and implemented the nested qualitative study and supervised the qualitative analysis. MC provided patient and public input in the design, implementation, and trial reporting. HC contributed to the protocol development, implementation, and co-ordination of the data acquisition. CF implemented the trial and contributed to the co-ordination of data acquisition and trial reporting. EAG contributed to the design of the trial. SH undertook operational delivery of the trial. DH contributed to the acquisition of health economic data. DPM provided patient and public advice to inform the design and trial reporting. TN and TS contributed to implementation of the trial. CAT provided data management input into the design and was responsible for the co-ordination of data acquisition. EJT contributed to the acquisition of qualitative data and trial reporting, under the supervision of FLB. AJF co-conceived and designed the ATLANTIS trial, was responsible for its overall implementation across Leeds Clinical Trials Research Unit, and supervised the statistical analysis. HAE co-conceived and designed the ATLANTIS trial, contributed to participant enrolment and data acquisition, and had overall responsibility in her role as co-chief investigator. ACF, AW-H, P-LO, AJF, and HAE drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript. AW-H and P-LO had full access to, and verified, all the data in the study. ACF, AJF, and HAE had final responsibility for the decision to submit for publication. AJF is guarantor.

Declaration of interests

ACF, MJR, and HAE report National Institute for Health and Care Research (NIHR) grant funding paid to their institutions. AW-H reports NIHR grant funding paid to her institution, being a Data Monitoring and Ethics Committee and Trial Steering Committee member of NIHR funded and Medical Research Council funded projects, and travel reimbursement for expert Committee membership of the Yorkshire and Northeast Regional Advisory Committee for NIHR Research for Patient Benefit. SLA reports NIHR, Yorkshire Cancer Research, and Health Data Research UK grant funding paid to her institution, consulting fees from West Yorkshire Integrated Care Board paid to her institution, speaker's payments from Xytal, and being a grant funding panel member for NIHR. RF reports NIHR and Yorkshire Cancer Research grant funding paid to his institution, and being a Chair of a NICE Implementation Strategy Group. EAG reports NIHR and Leeds Hospitals Charity grant funding paid to her institution. AJF reports NIHR grant funding paid to her institution, and reports being a Data Monitoring and Ethics Committee and Trial Steering Committee member of NIHR and BHF funded projects, and an NIHR senior investigator. All other authors declare no competing interests.

Data sharing

All data requests should be submitted to the corresponding author for consideration and would be subject to review by a subgroup of the trial team, which will include the data guarantor, Professor Amanda J Farrin. Access to anonymised data could be granted following this review. All data-sharing activities would require a data-sharing agreement.

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