**Title:** Amitriptyline at Low-dose and Titrated for Irritable Bowel Syndrome as Second-line Treatment (ATLANTIS): A Randomised Double-blind Placebo-controlled Trial in Primary Care.

**Short running head:** Amitriptyline as Second-line Treatment for Irritable Bowel Syndrome.

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**Abbreviations:** ASEC Antidepressant Side Effect Checklist

BDA British Dietetic Association

CI confidence interval

EMA European Medicines Agency

FDA Food and Drug Administration

GP general practitioner

HADS Hospital Anxiety and Depression Scale

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

IBS-SSS Irritable Bowel Syndrome Severity Scoring System

MCID minimum clinically important difference

NICE National Institute for Health and Care Excellence

NIHR National Institute for Health and Care Research

OR odds ratio

PHQ-12 Patient Health Questionnaire-12

PPI patient and public involvement

RCT randomised controlled trial

SD standard deviation

SGA subjective global assessment

TCA tricyclic antidepressant

WSAS Work and Social Adjustment Scale

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**Keywords:** irritable bowel syndrome; tricyclic antidepressant; abdominal pain; bowel habit; abdominal distension

**Word count:** 4997

**SUMMARY**

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

**Methods:** We did a randomised, double-blind, placebo-controlled trial (AmitripTyline at Low-dose ANd Titrated for Irritable bowel syndrome as Second-line treatment (ATLANTIS)) at 55 general practices in the UK. Eligible participants were aged 18 years or over with Rome IV IBS of any subtype, and ongoing symptoms (IBS Severity Scoring System (IBS-SSS) score 75 points or more) 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 (10mg once daily) or placebo for 6 months, with dose titration over 3 weeks (up to 30mg once daily), according to symptoms and tolerability. Participants, their general practitioners (GPs), investigators, and the analysis team were all masked to allocation throughout the trial. The primary outcome was the IBS-SSS score at 6 months. A key secondary outcome was subjective global assessment (SGA) of relief of IBS symptoms at 6 months. Effectiveness analyses were according to intention-to-treat; safety analyses were according to treatment receipt. This trial is registered with the ISRCTN (ISRCTN48075063).

**Findings:** Between 18th October 2019 and 11th April 2022, 463 participants (mean age 48.5 years (SD 16.1 years), 315 (68%) female) were randomly assigned 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 arms at 6 months (-27.0; 95% CI -46.9 to -7.10, *p*=0.0079). Forty-six (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 amitriptyline, three placebo) and five serious adverse events unrelated to trial medication.

**Interpretation:** This is the largest trial of a TCA 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. GPs 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.

**Funding:** National Institute for Health and Care Research Health Technology Assessment Programme (grant reference: 16/162/01).

**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 anti-diarrhoeal 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 (GPs) should “consider” low-dose tricyclic antidepressants (TCAs) as a second-line treatment. We searched PubMed with the terms “irritable bowel syndrome”, “treatment”, and “tricyclic antidepressant” to identify articles published between January 1st, 1980, and May 23rd, 2023. We did not limit the search according to dose of TCA studied. We identified 168 articles reporting on this issue. Although several systematic reviews and meta-analyses report that TCAs 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 questions the generalisability of their findings to patients in this setting. In addition, the NICE guideline highlights the need for a trial of low-dose TCAs 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 the study**

To our knowledge, this is the largest trial of a TCA in IBS ever conducted, and the first based entirely in primary care. During 6 months of treatment, low-dose amitriptyline, titrated from 10mg o.d. to a maximum of 30mg o.d., 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 arm. 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. GPs 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.

**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 impact on both the individual and society. Patients with IBS may have impairments in quality of life of a similar magnitude to individuals with organic gastrointestinal conditions, such as Crohn’s disease,7 and worse than patients with other chronic non-gastrointestinal diseases, such as diabetes or heart failure.8 Work activity 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 $10 billion in the USA.13

Most patients with IBS are managed by general practitioners (GPs).14 First-line therapies in primary care, 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 anti-diarrhoeal drugs, although their efficacy is modest.16,17 When these are ineffective, the NICE guideline states that GPs should “consider” low dose tricyclic antidepressants (TCAs) for their analgesic effect as a second-line treatment, with “consider” meaning that any benefit is uncertain. However, less than 10% of GPs prescribe TCAs for IBS often, and only 50% believe they are effective.18 Given that 95% of GPs use TCAs to treat insomnia,19 it is presumably uncertainty over their efficacy in IBS, rather than concerns about side effects, that explains this.

Meta-analyses of randomised controlled trials (RCTs) suggest a benefit of TCAs,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 TCAs are effective in patients with IBS seen in primary care. Indeed, the NICE guideline highlights the need for a trial of TCAs 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 GPs prescribe commonly for other conditions,19 and has a well-characterised safety profile.29 We, therefore, did a RCT of amitriptyline in IBS in primary care.

**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 superiority trial of amitriptyline as second-line treatment for IBS in primary care, recruiting adults with IBS (Figure 1). The majority of participants recruited consented to 12-month study participation, consisting of an initial 6 months of trial medication with the option to continue this for a further 6 months. Treatment duration and follow-up was curtailed to 6 months for later recruits, due to protocol changes during the COVID-19 pandemic. A within-study cost-effectiveness 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 GP experiences of treatment and trial involvement will be reported separately. Patient and public involvement (PPI) 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 (ISRCTN48075063).

Eligible participants were 18 years and over 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, page 9).31 Participants had tried first-line treatments, as recommended by NICE,15 including dietary changes and lifestyle advice, soluble fibre, antispasmodics, laxatives, or anti-diarrhoeals, 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. Other inclusion criteria included: 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. Exclusion criteria included: age >60 years with no GP review in the 12 months prior to screening (to assess for organic 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 TCA.30 Eligible participants met all inclusion criteria and none of the exclusion criteria.

Potentially eligible patients were identified via SnoMed clinical terms searches of primary care records and invited to take part by letter, or opportunistically following a GP 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 GP and hub lead clinician.

**Randomisation and Masking**

Participants were assigned randomly (1:1) to receive amitriptyline or 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 arms 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, GPs, investigators, and the analysis team) were masked fully to treatment allocation prior to database lock, except for unblinded safety statisticians. Trial medication was supplied by Modepharma Limited 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 active treatment and placebo arms, and unique kit codes were used.

**Procedures**

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

We provided standardised written information (appendix, pages 2 to 5), developed with input from PPI representatives, to guide dose titration, advising participants to commence at a dose of 10mg (one tablet) at night with dose titration over 3 weeks, up to a maximum of 30mg 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 1 and 3 weeks to assess tolerability, it was expected most participants would reach a steady dose. However, participants could modify dose 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 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 consented to 12-month follow-up.

All participants completed electronic or postal questionnaires at baseline, and 3, 6, and 12 months, and answered a weekly question “Have you had adequate relief of your IBS symptoms?” for the entire 6-month study duration. Text message and e-mail reminders were sent to non-responders at 1-week to prompt completion, followed by a telephone call as a final reminder.

**Outcomes**

Full definitions of outcomes are provided in the appendix (pages 6 to 7). The primary outcome was the effect on global IBS symptoms, measured by the IBS-SSS,32 6 months after randomisation. 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 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 3 and 12 months, 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 at 6 months. We assessed IBS-associated somatic symptoms,38 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 3, 6, and 12 months.

**Statistical Analysis**

We estimated an evaluable sample size of 414 participants provided 90% power to detect a minimum clinically important difference (MCID) of 35 points between amitriptyline and placebo at 6 months on the IBS-SSS, proposed in a previous trial of cognitive behavioural therapy in IBS,42,43 assuming a maximum IBS-SSS standard deviation (SD) of 110 points,44,45 and 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 randomised, regardless of adherence. Similarly, for 12-month outcomes these were analysed in the intention-to-treat population, defined as all participants randomised 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 arm 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 data sets.46 Sensitivity analyses on the per protocol population (defined as participants who were not major protocol violators, received a full 6 months treatment, and adhered to trial medication; appendix, page 10), and on participants with complete data, tested robustness of results for the primary outcome. Results were expressed as point estimates, together with 95% confidence intervals (CIs) and *p*-values.

We analysed secondary binary (SGA of relief and acceptability) outcomes 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 3, 6, and 12 months including PHQ-12, HADS, and WSAS scores, as for the primary outcome, adjusted for the respective baseline score. We conducted pre-specified 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 regression, as appropriate (appendix, page 8). We conducted further pre-specified (and *post hoc* where indicated)exploratory moderator analyses to investigate if 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 arm 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 arm, and the total ASEC score was analysed using linear regression adjusted for true minimisation variables and available data for participants on treatment at 3 and 6 months.41 The number of participants reporting a serious adverse event, and details of all serious adverse events, were reported for each treatment group. The numbers of participants withdrawing from trial treatment were summarised by treatment arm, with reasons.

**Role of the Funding Source**

The study was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment Programme (grant reference: 16/162/01). The funder had no role in data collection, analysis, interpretation, writing of the manuscript, or the decision to submit for publication. This report is independent research in response to a commissioned call funded by the NIHR. The views expressed in this publication are those of the authors, not necessarily those of the National Health Service, the NIHR, or the Department of Health and Social Care.

**RESULTS**

Between 18th October 2019 and 11th April 2022, 15,672 potentially eligible patients were invited to take part and 1253 interested patients were screened (Figure 2). We randomised 463 (37% of those screened) participants (mean age 48.5 years (SD 16.1 years), 315 (68%) female), 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, page 11). Due to the COVID-19 pandemic, trial recruitment paused from March 2020 to July 2020, in line with national guidance. Trial follow-up completed in October 2022 with 6-month follow-up achieved for 401 (87%) participants (204 (88%) amitriptyline, 197 (85%) placebo) (appendix, page 12). Study withdrawals from optional interviews, monthly or weekly questionnaires, or from further data collection occurred in 23 (5%) participants. Fourteen (3%) participants (four (2%) low-dose amitriptyline, 10 (4%) placebo) took up the optional 1-month GP appointment. All participants assigned to treatment were included in intention-to-treat analyses. Protocol violations occurred in six (1%) participants; four were major violations and excluded from the per protocol analysis (appendix, page 10).

Participant demographics and baseline characteristics, IBS symptom severity, PHQ-12 scores, HADS-depression and HADS-anxiety scores, and previous first-line treatments were similar between arms (Table 1). Over 80% of participants had IBS-D or IBS-M, 84% had a normal HADS-depression score, and 85% 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 median duration of IBS was 10 years.

In total, 338 (73%) participants completed 6 months treatment; 173 (75%) in the amitriptyline arm and 165 (71%) allocated to placebo (appendix, page 13). There were 105 (23%) participants discontinuing trial medication before 6 months; 46 (20%) allocated to amitriptyline and 59 (26%) to placebo. The most common reason for discontinuation was adverse events in 30 (13%) participants allocated to amitriptyline and 20 (9%) to placebo, followed by lack of benefit in seven (3%) amitriptyline and 18 (8%) placebo. A further 17 (4%) participants were lost to follow-up and three (1%) did not commence treatment. Similar numbers of the 338 participants completing 6 months treatment in both arms reported making dietary modifications, changing their exercise regimen, or commencing a new drug for IBS, other than a TCA, during the trial (appendix, page 14). By 3 months, similar proportions of participants randomised to amitriptyline were taking 20mg (35%) or 30mg o.d. (38%), although by 6 months this increased to 43% taking 30mg o.d. However, in the placebo arm, 57% of participants titrated their dose to 30mg o.d. by 3 months and this remained similar at 6 months (appendix, page 15).

Amitriptyline was superior to placebo at 6 months in the intention-to-treat analysis for the primary outcome, with a significant difference in mean IBS-SSS score between arms (-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 (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 25 weeks (OR = 1.56; 95% CI 1.20 to 2.03, *p*=0.0008) (Table 2, appendix, page 22), and an increased proportion of participants reporting relief for ≥13 of 25 weeks (90/222 (41%) vs. 67/221 (30%)). Overall, more participants found amitriptyline acceptable and would have been willing to continue taking it at 6 months (OR = 1.60; 95% CI 1.08 to 2.35, *p*=0.018). Adherence at 3 months was identical between treatment arms, but by 6 months it was generally higher in the amitriptyline arm (172/232 (74%) vs. 155/228 (68%)). There was no evidence of an effect on PHQ-12 scores at 6 months, or HADS-anxiety. HADS-depression, or WSAS scores at either 3 or 6 months (Table 2).

In our pre-specified exploratory outcomes (appendix, pages 16, 23, and 24), there was an increased odds with amitriptyline for IBS-SSS to reduce by at least 50 points at both 3 months (OR = 1.49; 95% CI 0.97 to 2.28, *p*=0.068) and 6 months (OR = 1.48; 95% CI 0.97 to 2.27, *p*=0.068), but this was not statistically significant. Significantly more participants allocated to amitriptyline experienced a ≥30% decrease in abdominal pain severity on the IBS-SSS at 6 months (OR = 1.66; 95% CI 1.12 to 2.46, *p*=0.012) but not abdominal distension severity. Using an alternative definition of SGA of relief of IBS symptoms, where only those reporting considerable or complete relief at 3 or 6 months were considered responders, an increase in the effect size for amitriptyline was observed at both 3 (OR = 1.81; 95% CI 1.17 to 2.79) and 6 months (OR = 1.88; 95% CI 1.20 to 2.95); 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 pre-specified and *post hoc* exploratory moderator analyses see appendix, pages 1, 18 to 21, and 27 to 35.

Table 3 reports treatment-emergent adverse events at 3 and 6 months, as captured by the ASEC for participants still on treatment. There was a statistically significant increase in the total ASEC score with amitriptyline compared with placebo at 3 months (1.39; 95% CI 0.29 to 2.50, *p*=0.013) but not 6 months (0.26; 95% CI -0.98 to 1.51, *p*=0.68). Excess adverse events with amitriptyline related mainly to its known anticholinergic effects, including dry mouth, drowsiness, blurred vision, and urination problems. However, rates fell generally between 3 and 6 months and few (<5%) were severe, except for constipation and diarrhoea (<10%) (appendix, pages 26 and 26). For adverse events leading to treatment discontinuation, see appendix page 17. There were five serious adverse reactions (two amitriptyline, three placebo) and five serious adverse events unrelated to trial medication (four amitriptyline, one placebo).

**DISCUSSION**

To our knowledge, this is the largest trial of a TCA in IBS ever undertaken and the first based entirely in primary care. 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 3 and 6 months, compared with baseline, and 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 than placebo and almost three-quarters adhered to the drug during the 6-month trial. Adverse events were more frequent with low-dose amitriptyline. Those reported in participants receiving amitriptyline in excess of those reported by the placebo arm mainly related to its anticholinergic effects, including drowsiness and dry mouth. However, for most participants, these were judged as mild, although withdrawals 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 (EMA) 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 accepted widely 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 Food and Drug Administration (FDA) and EMA recommendations for drug trials in IBS.47,49 This 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% 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 and EMA-recommended endpoints and are more stringent but did not require completion of a daily diary outcome specific to IBS subtype. Those recruited were not ethnically diverse, despite considerable efforts to reach out to ethnic minorities 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 may 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 arm, there is the possibility that some participants guessed correctly they were receiving active drug, and this has influenced findings.

The Rome IV criteria select 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 may appear relatively high, and the 35-point MCID was not met, although the 95% CI included 35 points and excluded the possibility of no effectiveness of amitriptyline. In terms of the latter, the MCID was derived from a pilot trial,51 and although used as an endpoint and achieved in a trial of cognitive behavioural therapy in IBS,43 this was in comparison with treatment as usual and participants were not blinded, so knew whether they received active treatment. ATLANTIS was blinded 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 BDA dietary advice sheet to all participants, regular follow-up, usual GP care throughout, and telephone calls from a research nurse to assist with dose titration and trial medication re-issue. However, numbers of participants reporting making dietary changes or commencing a new drug for IBS were relatively small, and similar between treatment arms. Participants may 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 TCAs 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 desipramine 150mg o.d., recruiting a mixed population of 216 female patients with functional bowel disorders, 172 of whom had IBS.54 Similar to our trial, the commonest side effects related to the anticholinergic effects of the drug. More patients discontinued desipramine due to adverse events than in our trial, which may 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 amitriptyline 10mg o.d. were 70%, compared with 41% with placebo, but this was not statistically significant, likely due to an underpowered RCT. Adverse event rates were similar between treatment arms.

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 men. The magnitude of the difference in treatment effect increased between 3 and 6 months, and remained similar at 12 months, although this was no longer statistically significant, underlining the importance of allowing adequate time for low-dose amitriptyline to have a beneficial effect in IBS and 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 arm. It may 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 12-month 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 summary, this trial of low-dose amitriptyline, 10 to 30mg o.d., 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 TCA 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. GPs 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 need to change to reflect these findings.

**ACKNOWLEDGEMENTS**

The study was funded by the NIHR Health Technology Assessment Programme (grant reference: 16/162/01). The funder had no role in data collection, analysis, interpretation, writing of the manuscript, or the decision to submit for publication. This report is independent research in response to a commissioned call funded by the NIHR. The views expressed in this publication are those of the authors, not necessarily those of the National Health Service, the NIHR, or the Department of Health and Social Care.

We would like to thank the 463 participants and the 55 general practices involved in the study, as well as the Trial Steering Committee and Data Monitoring and Ethics Committee for their support throughout.

**AUTHORS CONTRIBUTIONS**

ACF 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 contributed to the design of the trial, participant enrolment, and data acquisition. RF contributed to the design of the trial, participant enrolment, and data acquisition. FLB designed and implemented the nested qualitative study and supervised the qualitative analysis. MC provided PPI input in the design, implementation, and trial reporting. HC contributed to the protocol development, implementation, and co-ordination of the data acquisition. DC contributed to participant enrolment and 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 . AH contributed to participant enrolment and data acquisition. DH contributed to the acquisition of health economic data. DPM provided PPI advice to inform the design and trial reporting. TN contributed to implementation of the trial. SN contributed to participant enrolment and data acquisition. CMT 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. RT contributed to participant enrolment and data acquisition. AJF conceived and designed the ATLANTIS trial, was responsible for its overall implementation across Leeds Clinical Trials Research Unit and supervised the statistical analysis. HAE 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 commentedon 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**

Alexander C. Ford: NIHR grant funding paid to his institution. Alexandra Wright-Hughes: NIHR grant funding paid to her institution, Data Monitoring and Ethics Committee and Trial Steering Committee member of NIHR and MRC funded projects, travel reimbursement for expert Committee membership of the Yorkshire and Northeast Regional Advisory Committee for NIHR Research for Patient Benefit. Sarah L. Alderson: NIHR, YCR, 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 grant funding panel member for NIHR. Pei-Loo Ow: none. Matthew J. Ridd: NIHR grant funding paid to his institution. Robbie Foy: NIHR and YCR grant funding paid to his institution, Chair of NICE Implementation Strategy Group. Gina Bianco: none. Felicity L. Bishop: none. Matthew Chaddock: none. Heather Cook: none. Deborah Cooper: none. Catherine Fernandez: none. Elspeth A. Guthrie: NIHR and Leeds Hospitals Charity grant funding paid to her institution. Suzanne Hartley: none. Amy Herbert: none. Daniel Howdon: none. Delia P. Muir: none. Taposhi Nath: none. Sonia Newman: none. Thomas Smith: none. Christopher M. Taylor: none. Emma J. Teasdale: none. Ruth Thornton: none. Amanda J. Farrin: NIHR grant funding paid to her institution, Data Monitoring and Ethics Committee and Trial Steering Committee member of NIHR and BHF funded projects, and NIHR senior investigator. Hazel A. Everitt: NIHR grant funding paid to her institution.

**ETHICS COMMITTEE APPROVAL**

The final protocol and subsequent amendments were approved by Yorkshire and the Humber (Sheffield) Research Ethics Committee (19/YH/0150).

**DATA SHARING STATEMENT**

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 may be granted following this review. All data-sharing activities would require a data-sharing agreement.

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**Figure 1. Study Design.**

**Figure 2. Flow of Participants Through the Trial.**

**Figure 3. Key Secondary Outcome of SGA of Relief of IBS Symptoms at 6 Months.**

**Table 1. Baseline Demographics and Characteristics of Participants.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Low-dose amitriptyline**  **(n = 232)** | **Placebo**  **(n = 231)** | **All participants**  **(n = 463)** |
| **Mean age (SD)** | 49.2 (16.2) | 47.8 (15.9) | 48.5 (16.1) |
| **Female sex (%)** | 156 (67) | 159 (69) | 315 (68) |
| **White ethnicity (%)** | 226 (97) | 225 (97) | 451 (97) |
| **IBS subtype (%)**  IBS-C  IBS-D  IBS-M  IBS-U | 40 (17)  92 (40)  93 (40)  7 (3) | 37 (16.0)  89 (39)  98 (42)  7 (3) | 77 (17)  181 (39)  191 (41)  14 (3) |
| **Hub (%)**  West Yorkshire  West of England  Wessex | 43 (19)  92 (40)  97 (42) | 44 (19)  92 (40)  95 (41) | 87 (19)  184 (40)  192 (42) |
| **IMD quintile (%)\***  1  2  3  4  5 | 13/229 (6)  34/229 (15)  38/229 (17)  75/229 (33)  69/229 (30) | 13/230 (6)  27/230 (12)  33/230 (14)  74/230 (32)  83/230 (36) | 26/459 (6)  61/459 (13)  71/459 (16)  149/459 (33)  152/459 (33) |
| **Median years from IBS diagnosis (IQR)** | 10 (4, 21) | 9 (4, 18) | 10 (4, 20) |
| **Mean IBS-SSS (SD)†** | 273.4 (90.5) | 272.1 (90.3) | 272.8 (90.3) |
| **IBS-SSS severity (%)‡**  Mild (75-174)  Moderate (175-299)  Severe (300-500) | 37 (16)  98 (42)  94 (41) | 26 (11)  103 (45)  97 (42) | 63 (14)  201 (43)  191 (41) |
| **Mean PHQ-12 score (SD)†** | 6.3 (3.5) | 6.3 (3.6) | 6.3 (3.5) |
| **Mean HADS-anxiety score (SD)†** | 7.3 (4.3) | 7.7 (4.3) | 7.5 (4.3) |
| **HADS-anxiety score ≥8 (%)** | 106 (46) | 112 (49) | 218 (47) |
| **Previously treated for anxiety (%)** | 80 (34) | 79 (34) | 159 (34) |
| **Mean HADS-depression score (SD)†** | 4.4 (3.6) | 4.1 (3.2) | 4.3 (3.4) |
| **HADS-depression score ≥8 (%)** | 37 (16) | 36 (16) | 73 (16) |
| **Previously treated for depression (%)** | 79 (34) | 99 (43) | 178 (38) |
| **Mean WSAS score (SD)†** | 11.2 (8.2) | 11.5 (7.6) | 11.4 (7.9) |
| **Previous dietary changes (%)** | 232 (100) | 231 (100) | 463 (100) |
| **Previous first-line treatments (%)⁑**  Antispasmodics  Anti-diarrhoeals  Fibre supplements  Laxatives  Peppermint oil | 232 (100)  176 (76)  70 (30)  52 (22)  51 (22)  18 (8) | 231 (100)183 (79)  75 (33)  52 (23)  34 (15)  27 (12) | 463 (100)359 (78)  145 (31)  104 (23)  85 (18)  45 (10) |

\*Index of mean deprivation; quintile 1 = neighbourhood in the 20% most deprived neighbourhoods in England, 2 = 20-40%, 3 = 40-60%, 4 = 60-80%, 5 = neighbourhood in the 20% least deprived neighbourhoods in England.

†Lower scores are better.

‡Eight participants with an IBS-SSS ≥75 points at eligibility screening had a score <75 points at the time of randomisation but were included as they met eligibility criteria at screening.

⁑Not mutually exclusive.

**Table 2. Primary Outcome at 6 Months and Secondary Outcomes at 3 and 6 Months.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **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\*** |
| **IBS-SSS†**  Mean total IBS-SSS (SD)‡  Change in IBS-SSS from baseline (SD) | 173.0 (106.6),  n = 219  -99.8 (107.7) | 194.6 (107.5),  n = 213  -76.1 (107.1) | -23.3 (-42.0, -4.6), *p* = 0.014  -- | 170.4 (107.7),  n = 204  -99.2 (112.9) | 200.1 (114.5),  n = 197  -68.9 (109.3) | -27.0 (-46.9, -7.1), *p* = 0.0079  -- |
| **SGA of relief of IBS symptoms (%)⁑** | 139/220 (63) | 105/213 (49) | 1.70 (1.15, 2.53),  *p* = 0.0080 | 125/204 (61) | 88/195 (45) | 1.78 (1.19, 2.66),  *p* = 0.0050 |
| **Adequate relief of IBS symptoms over 25 weeks (%)§** | -- | -- | -- | 90/222 (41) | 67/221 (30) | 1.56 (1.20, 2.03), *p* = 0.0008 |
| **Mean PHQ-12 score (SD)†** | -- | -- | -- | 5.7 (3.4),  n = 202 | 5.9 (3.2)  n = 192 | -0.04 (-0.58, 0.49), *p* = 0.88 |
| **Mean HADS-anxiety score (SD)†** | 6.5 (4.4),  n = 220 | 6.6 (4.0),  n = 212 | 0.05 (-0.53, 0.63), *p* = 0.86 | 6.7 (4.4),  n = 203 | 6.9 (4.0),  n = 193 | 0.08 (-0.49, 0.65), *p* = 0.78 |
| **Mean HADS-depression score (SD)†** | 3.5 (3.3),  n =220 | 3.6 (3.2),  n = 212 | -0.22 (-0.71, 0.26), *p* = 0.37 | 3.9 (3.6),  n = 202 | 4.0 (3.5),  n = 193 | -0.20 (-0.75, 0.34), *p* = 0.46 |
| **Mean WSAS score (SD)†** | 9.3 (7.6),  n = 210 | 9.5 (6.3),  n = 198 | -0.27 (-1.36, 0.83), *p* = 0.63 | 8.1 (7.6),  n = 195 | 9.4 (7.8),  n = 184 | -1.04 (-2.30, 0.23), *p* = 0.11 |
| **Acceptability of treatment (%)** | -- | -- | -- | 122/211 (58) | 100/213 (47) | 1.60 (1.08, 2.35),  *p* = 0.018 |
| **Adherence to treatment (%)⁋** | 193/232 (83) | 183/220 (83) | -- | 172/232 (74) | 155/228 (68) | -- |

\*Effect represents the mean difference between treatment arms 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.

§n/N (%) indicates the number of participants with adequate relief for ≥13 of 25 weeks, whereas effect indicated odds of relief across all 25 weeks with amitriptyline relative to placebo estimated from a generalised linear marginal mixed model of weekly data.

⁋Defined as “On medication every day or nearly every day” or “Half the days or more than half the days”. Proportional odds assumption not satisfied, descriptive analysis only.

**Table 3. Overview of Treatment-emergent Adverse Events at 3 and 6 Months in the Safety Analysis Set.**

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

\*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 30mg 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.