Low-dose titrated amitriptyline as second-line treatment for adults with irritable bowel syndrome in primary care: the ATLANTIS RCT

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Scientific summary

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Scientific summary

Background

Irritable bowel syndrome (IBS) affects 5% of the population, accounting for > 3% of all consultations in primary care in England and Wales. Symptoms include abdominal pain in association with a change in stool form or frequency. The condition impacts on quality of life and ability to work and limits social activities. The medical management of IBS is unsatisfactory, with no therapy proven to alter the long-term natural history and, at best, modest symptom reduction. Previous meta-analyses of trials conducted in secondary and tertiary care suggest low-dose tricyclic antidepressants (TCAs) may be efficacious, probably because of their pain-modifying properties, as well as their influence on gut motility, rather than any effects on mood. Although National Institute for Health and Care Excellence guidelines for the management of IBS in primary care suggest considering low-dose TCAs as second-line treatment, their effectiveness in this setting is unknown and they are infrequently prescribed by general practitioners (GPs).

Objectives

Our objective was to determine the clinical and cost-effectiveness of low-dose titrated amitriptyline compared with placebo for 6 months as a second-line treatment in adults with IBS in primary care.

Methods

ATLANTIS was a pragmatic, randomised, multicentre, parallel-group, two-arm, double-blind, placebo-controlled trial. A nested, qualitative study explored participant and GP experiences of treatments and trial participation. A within-study cost-effectiveness analysis was planned but, due to the coronavirus disease discovered in 2019 (COVID-19) pandemic, health economic analyses were removed after obtaining additional funding to complete the trial to prioritise funds for participant recruitment. These will be subject to further funding. Participants, their GPs, investigators, the research team, and the analysis team were all masked to treatment allocation throughout the trial. Patients meeting Rome IV criteria for IBS who had tried first-line treatments and with ongoing IBS symptoms [score of ≥ 75 on the IBS Severity Scoring System (IBS-SSS)] were recruited via mail-out from 55 general practices in three regions in England. Participants were randomised 1 : 1 to receive either low-dose titrated amitriptyline or placebo. Both treatments were supplied for 6 months, with the dose commenced at 10 mg o.d. and titrated to a maximum of 30 mg o.d. or a minimum of 10 mg alternate days. Dose titration was participant-led according to IBS symptoms and side effects, with support from the trial team and a dose titration document developed with input via patient and public involvement. Participants recruited earlier to the trial had the option to continue blinded treatment for an additional 6 months.

The primary outcome was the effect of amitriptyline on global IBS symptom scores at 6 months. The key secondary outcome was the proportion of participants with relief of IBS symptoms at 6 months. Other secondary outcomes included effect on global IBS symptoms and relief of IBS symptoms at 3 and 12 months, effect on IBS-associated somatic symptoms at 6 months, effect on quality of life, anxiety, and depression scores, and ability to work and participate in other activities at 3, 6 and 12 months, as well as acceptability and tolerability of, and adherence to, treatment.

Patient-reported questionnaires at baseline and 3, 6 and 12 months post randomisation (unless otherwise indicated) were used to assess IBS symptom severity (measured via the IBS-SSS), relief of IBS symptoms [measured by subjective global assessment (SGA) of relief], adequate relief of IBS symptoms

(measured by a weekly response to the question 'Have you had adequate relief of your IBS symptoms?'), IBS-associated somatic symptoms [using the Patient Health Questionnaire-12 (PHQ-12)], mood [using the Hospital Anxiety and Depression Scale (HADS)], ability to work and participate in other activities [using the Work and Social Adjustment Scale (WSAS)], quality of life (using the EQ-5D-3L), healthcare use (using a bespoke health resource use questionnaire), and tolerability [using the Antidepressant Side-Effect Checklist (ASEC)]. Numbers of participants reporting serious adverse events (SAEs), including serious adverse reactions (SARs), were reported for each treatment group.

An evaluable sample size of 414 participants would provide 90% power to detect a minimum clinically important difference of 35 points between amitriptyline and placebo at 6 months on the IBS-SSS. This 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. We planned to recruit 518 participants, allowing for 20% loss to follow-up. Effectiveness outcomes were analysed in the intention-to-treat population, defined as all participants randomised, regardless of adherence. All statistical testing used two-sided 5% significance levels. The primary outcome was analysed using a linear regression model, adjusted for minimisation variables and baseline IBS-SSS score. Missing data were imputed by treatment arm, via multiple imputation, and results were expressed as point estimates with 95% confidence intervals (CIs). Secondary binary outcomes were analysed in logistic or ordinal regression models, with results expressed as odds ratios (ORs) with 95% CIs. Continuous secondary outcomes, including PHQ-12, HADS and WSAS scores, were analysed as for the primary outcome, adjusted for the respective baseline score. All participants receiving at least one dose of trial medication, according to medication received, were included in the safety analysis.

The nested, qualitative study aimed to identify factors that would facilitate or impede prescribing of, acceptability of, and adherence to, low-dose amitriptyline in IBS, to identify participants' and GPs' perspectives on the broader impact of the trial, and to explore psychosocial and contextual factors that might shape wider use of amitriptyline for IBS. Familiarity with amitriptyline may both hinder uptake, given its association with depression, and facilitate it, given that it is a known drug, taken in a low dose distinct from the antidepressant dose, already used for a range of other painful conditions and has comparatively mild, and in some cases potentially beneficial, side effects such as on sleep. Semi-structured audio-recorded telephone interviews were conducted with a diverse sub-sample of trial participants and GPs involved in the trial and transcribed verbatim. The final sample size was dependent on saturation, to achieve a rigorous, credible analysis in relation to the aims. Topic guides allowed flexible exploration of all required topics, while remaining open to participants' individual experiences and perspectives. To enhance trustworthiness of the analysis, all qualitative study team members contributed to avoid producing idiosyncratic interpretations, a negative case analysis was undertaken, and an audit trail was produced to enhance transparency, including detailed coding manuals and interviewer field notes. Reflexive thematic analysis, incorporating techniques from grounded theory, was used to analyse the qualitative data. Data collection and initial analyses proceeded iteratively, and informed subsequent interviews. Analysis was primarily inductive, with researchers identifying themes in the data rather than imposing any pre-existing interpretive framework. Qualitative findings were related to the main trial findings by comparing themes across subgroups and against the quantitative data.

Clinical results

In total, 15,672 potentially eligible patients were invited to take part, of whom 1253 were interested and were screened. Of those screened, 463 (37.0%) were randomised {mean age 48.5 years [standard deviation (SD) 16.1 years], 315 (68.0%) female}, to amitriptyline (n = 232) or placebo (n = 231). Six-month follow-up was achieved for 401 (86.6%) participants, 204 (87.9%) in the amitriptyline arm, and 197 (85.3%) in the placebo arm. Participants were well balanced between treatment arms according to demographics and baseline characteristics, IBS symptom severity, PHQ-12 scores, HADS-depression and HADS-anxiety scores, and previous first-line treatments. Among participants, 80.4% had IBS-D or

IBS-M, 84.2% had a normal HADS-depression score, and 84.7% had moderate to severe scores on the IBS-SSS, with a mean IBS-SSS score in all participants of 272.8 (SD 90.3). The median duration of IBS was 10 years.

In total, 338 (73.0%) participants completed 6 months of treatment, 173 (74.6%) randomised to amitriptyline and 165 (71.4%) to placebo. Discontinuation of trial medication before 6 months occurred in 105 (22.7%) participants, 46 (19.8%) allocated to amitriptyline and 59 (25.5%) to placebo. The most common reason for discontinuing trial medication was adverse events (AEs) in 30 (12.9%) participants allocated to amitriptyline and 20 (8.7%) to placebo, followed by lack of benefit in 7 (3.0%) randomised to amitriptyline and 18 (7.8%) to placebo. There were a further 17 (3.7%) participants lost to follow-up and 3 (0.6%) who did not commence trial medication. By 3 months, similar proportions of participants randomised to amitriptyline had titrated their dose to 20 mg o.d. (35.2%) or 30 mg o.d. (37.8%), although by 6 months this had increased to 42.8% taking 30 mg o.d. However, in the placebo arm, 57.0% of participants titrated their dose to 30 mg o.d. within 3 months and this proportion was similar at 6 months.

For the primary outcome, amitriptyline was superior to placebo at 6 months in the intention-to-treat analysis, with a significant difference in mean IBS-SSS score between arms (−27.0, 95% CI −46.9 to −7.1; $p = 0.008$). For the key secondary outcome, SGA of relief of IBS symptoms, amitriptyline was also superior to placebo (OR for relief of IBS symptoms = 1.78, 95% CI 1.19 to 2.66; $p = 0.005$). At 3 months, the difference in mean change in IBS-SSS score also favoured amitriptyline (−23.3, 95% CI −42.0 to −4.6; $p = 0.014$), as did the SGA of relief of IBS symptoms (OR = 1.70, 95% CI 1.15 to 2.53; $p = 0.008$). In a sensitivity analysis using an alternative definition of SGA of relief of IBS symptoms, where only those reporting considerable or complete relief of IBS symptoms at 3 or 6 months were classed as responders, the effect size in the amitriptyline arm increased 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). Other 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.

In terms of adequate relief of IBS symptoms, amitriptyline was also superior to placebo with increased odds of adequate relief across all 25 weeks (OR = 1.56, 95% CI 1.20 to 2.03; $p < 0.001$), and a higher proportion of participants reporting adequate relief for ≥ 13 of 25 weeks [90/222 (40.5%) vs. 67/221 (30.3%)]. Significantly higher numbers of participants taking amitriptyline reported the drug to be 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 in the two treatment arms, but it was higher in the amitriptyline arm at 6 months [172/232 (74.1%) vs. 155/228 (68.0%)]. Amitriptyline had no significant effect on PHQ-12 scores at 6 months, or HADS-anxiety, HADS-depression or WSAS scores at either 3 or 6 months.

In terms of treatment-emergent AEs, there was a statistically significant increase in the total ASEC score in those receiving amitriptyline compared with placebo at 3 months (1.39, 95% CI 0.29 to 2.50; $p = 0.013$) but not at 6 months (0.26, 95% CI −0.98 to 1.51; $p = 0.681$). The AEs reported in participants receiving amitriptyline in excess of those reported by the placebo arm mainly related to its known anticholinergic effects, including dry mouth, drowsiness, blurred vision and problems with urination. However, rates of treatment-emergent AEs fell between 3 and 6 months and few were severe. The commonest AEs leading to discontinuation in the amitriptyline arm were drowsiness and deterioration of mood. In total, there were five SARs, two in the amitriptyline arm and three in the placebo arm. There were five SAEs unrelated to trial medication, of which four occurred in the amitriptyline arm and one in the placebo arm.

In the subset of participants recruited to 12 months' follow-up and with the choice to continue treatment beyond 6 months, 44% of participants completed 12 months' treatment. Despite the mixed sample, in the 12-month ITT population, weak evidence of a significant effect in favour of low-dose

amitriptyline remained on the mean IBS-SSS (−22.6, 95% CI −49.35 to −4.16; $p = 0.098$) and the SGA of relief of global IBS symptoms (OR = 1.58, 95% CI 0.94 to 2.64; $p = 0.083$). In contrast to 6-month results, there was a statistically significant effect on the HADS-depression (−0.88, 95% CI −1.71 to 0.06; $p = 0.036$) and WSAS (−2.14, 95% CI −3.80 to −0.49; $p = 0.011$) scores in favour of low-dose amitriptyline.

Qualitative results

The qualitative study conducted and thematically analysed 77 semistructured interviews with 42 participants and 16 GPs. A multidisciplinary team including patient collaborators explored multiple aspects of participants' and GPs' experiences of treatments and participating in the ATLANTIS trial.

The qualitative analysis of barriers and facilitators suggests that low-dose amitriptyline for IBS is acceptable to, and is often welcomed by, GPs and patients as an additional treatment option. Addressing concerns and promoting facilitators could facilitate wider use of low-dose amitriptyline for IBS which may be achieved through:

- Clear communication to clinicians, for example in clinical guidelines, that distinguishes low-dose amitriptyline for IBS from amitriptyline use for other conditions (especially depression).
- Resources to support GP–patient communication to distinguish low-dose amitriptyline for IBS from amitriptyline for other conditions (especially depression). This might include, for example, tips for GPs when discussing amitriptyline for IBS with patients, online materials to support or reinforce messages given during consultations, tailored packaging and patient inserts, and education for pharmacists.
- Clear guidance about low-dose amitriptyline for IBS and anticholinergic burden. This should highlight that low-dose amitriptyline has lower potential risk and that currently anticholinergic burden risk scores do not account for dose, so can overinterpret risk with low-dose amitriptyline.
- Guidance and resources for GPs and patients to support patients managing their own dose titration. The dose-titration document used in ATLANTIS was well received by GPs and patients.

Conclusions

In 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. The results of ATLANTIS strongly support use of titrated low-dose amitriptyline 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.

Trial registration

This trial is registered as ISRCTN48075063.

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This article

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